POLYCYTHEMIA

Physiology, Diagnosis and Treatment
Based on 303 Cases



Classic picture in polycythemia vera. The color of the skin has a distinctly pinkish cast and is less blue than that observed in other cyanotic conditions.



The blue cyanosis associated with oxygen unsaturation of the blood. This patient had polycythemia secondary to the tetrology of Fallot.

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By JOHN H. LAWRENCE, M.D., D.Sc., F.A.C.P.

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Professor of Medical Physics and
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To my wife AMY and
MARK, SHELLEY and JIMMIE

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Contents

Preface

Polycythemia—whether primary (polycythemia vera) or secondary, such as that observed in certain cardiac and pulmonary conditions or seen in residents of high altitudes—is sufficiently rare so that many physicians do not have a wide experience in the study and treatment of these various types. Since the author has had an intensive experience in the study, diagnosis and treatment of various forms of polycythemia and since the differential diagnosis and treatment of the various types often present difficult problems, it has been urged by various colleagues that these experiences be put into book form with the hope that they might be of assistance to those physicians and workers who are less often confronted with the problem. This seems particularly important in view of the fact that at the present time there is a satisfactory method for the treatment of polycythemia vera.

The experiences and studies summarized here have been in many instances made possible only through the collaboration and assistance of many of the author's colleagues who over a period of twenty years have worked with him in the Donner Laboratory and Radiation Laboratory of the University of California. Most of these contributions are already recorded in the literature. Two colleagues, Drs. Nathaniel I. Berlin and Rex L. Huff, have made especially important contributions to our understanding and treatment of this condition. It is not possible to acknowledge the help of all who have worked with me, but some of these are: Drs. John J. Bertrand, Max Biggs, James L. Born, Ezra Bridge, William Chew, Alexander Contopoulo, R. Lowry Dobson, Ray Dunn, Paul J. Elmlinger, Lowell Erf, Anne Coetzel, John W. Gofman, Joseph Hamilton, Louis Hempelmann, Grace Hyde, Hardin Jones, B. V. A. Low-Beer, S. P. Masouredis, Rollin K. McCombs, Theodore C.

Prentice, Robert L Rosenthal Leonard Rubin, Louis Wasserman and John Weaver In the early days of the work, Dr Martin Kamen was of great assistance to the author and generously prepared the first artificially radioactive solutions used in therapy Professor Ernest O Lawrence made it possible to produce the radioactive phosphorus in the cyclotron in the early days and has always supported and encouraged the work of the author and his associates Dr Cornelius A Tobias has been of constant help as Chief Biophysicist of the Donner Laboratory The author is grateful to all of his colleagues and the many others who have helped from time to time in the care of patients Finally I want to thank Miss June Armstrong for her expert assistance in the many details of preparing this book for publication

For the studies reported here and the many related investigations reported in the medical literature during the past twenty years the author has had support from the Rockefeller Foundation the Markle Foundation The Macy Foundation, the Columbia Foundation of San Francisco the Donner Foundation Mrs Henry Stevens Kiersted Mr Robert Donner Mr Huntington Hartford an Anonymous Donor through the Chase National Bank and more recently the U S Public Health Service and the Atomic Energy Commission

J H L

Berkeley March 1955

Introduction

POLYCYTHEMIA refers to an increase in the number of red cells in the blood It may be secondary to hypoxia or associated with the condition called polycythemia vera *Vaquez and Osler* first described patients suffering from the complex we now call polycythemia vera [1, 2] Even though we are now able to treat this condition satisfactorily [3, 4] there is much yet to be learned regarding its nature and physiology Since the original observations of Vaquez and Osler numerous articles have appeared reporting further cases and special studies on physiology pathology and treatment There are no observations of large groups in which prognosis and length of life after various forms of therapy are reported in the literature There are however several excellent reports of treatment with radioactive phosphorus spray x irradiation and miscellaneous methods [5-10] For the literature prior to 1928 one may refer to the review by Harrop [11] This book is based on the author's experience with 231 patients with polycythemia vera Also included are studies of 72 patients with secondary and relative polycythemia and the relation of these conditions to polycythemia vera None of these conditions are common but when the physician is confronted with an increased red cell count it becomes important to determine which form of polycythemia is present

CHAPTER I

Polycythemia Vera

Clinical Picture

In polycythemia vera there is a marked and persistent elevation *in the total number of red cells in the circulation* commonly with ruddy cyanosis splenomegaly leukocytosis and thrombocytosis for which no etiology has been found The onset is usually insidious and the symptoms and signs are many and varied Some of the more common are headaches pains and aches in the body and extremities redness of the face lips and hands loss of memory, scotomata fatigability attacks of mental depression dyspnea on mild exertion tinnitus and dizziness[12] Tinney and co workers[13] demonstrated a peptic ulcer roentgenographically in 7 per cent of 163 polycythemia vera patients This is similar to the incidence of 10 per cent of Rosenthal and Bassen[14] The physical findings include the bluish red color of the skin and mucous membranes in contrast to the blue cyanosis associated with secondary polycythemia The liver is palpably enlarged in about 25 per cent of the cases and the spleen in 66 per cent[15] The blood pressure is elevated in 40 per cent of the patients[16] The laboratory tests reveal an elevated red cell count associated with an elevated hematocrit and elevated total red cell volume[17] a normal or near normal arterial oxygen saturation[18] and usually elevated white cell and platelet counts[3, 4] Thus the clinical picture is not difficult to recognize particularly when there is a palpably enlarged spleen Gaisbock described a subgroup of patients who apparently had a polycythemia with hypertension but without splenomegaly[19]

Physiology

The physiological mechanisms involved in polycythemia are somewhat understood where there is a known anoxic stimulus to red cell production such as occurs in some cases of cardiac and pulmonary disease and in individuals living at high altitude in whom red cell counts of 7 000 000 or more are commonly observed The studies of Hurtado and his associates in Peru [20] of Talbott [21] and our own investigations during two expeditions to the Andes [2] show the correlation between the degree of polycythemia and the altitude of residence However dwellers at high altitude do not have enlargement of the spleen or elevation in white cell or platelet counts Of interest in this connection is the work of Tinsley and co workers [22] who have shown the relationship between arterial oxygen content and red cell production by studying reticulocyte response and radioactive iron uptake in the red cells of patients subjected to various degrees of hypoxia or superoxia There is no known anoxic stimulus in the case of polycythemia vera however The studies of Harrop and Heath[24] suggest the possibility of some abnormality in gas transfer across the pulmonary alveoli but this does not seem proved [2] Numerous other studies such as those on red cell fragility [6] basal metabolism [7] *and bone marrow* [8 9 10] *have failed to shed light on the etiology* of polycythemia vera The fact that many of the patients reported in the past have developed a complicating leukemia supports the concept of the neoplastic nature of the condition but this adds little to our basic understanding [2 14 21 35] Minot and Buckman[26] reported that in a group of 15 patients with polycythemia vera 3 developed a complicating leukemia Their report is typical of others[8 9 28 38] in which the incidence of leukemia in patients with polycythemia vera was nearly 20 per cent Some authors believe that if patients with polycythemia vera live long enough all of them will eventually develop

leukemia In this connection it is of interest to quote from the early writings of a distinguished London physician[39] Dr F Parkes Weber says In regard to the persistent high leucocyte counts in this and many erythraemic cases I would express my views as follows I have regarded erythraemia as a syndrome caused by a primary neoplastic condition in the erythroblastic portion of the bone marrow analogous to myelosis (myeloid leukaemia) in the leucoblastic portion, but non malignant It has however gradually become clear that if this view is correct the high leucocyte count (chiefly due to excess of the polymorphonuclear neutrophils) found in many or most cases of erythraemia (the leucocyte count is not rarely 20 000 to 30 000) must signify that the non malignant neoplastic condition of the erythroblastic portion of the bone marrow is accompanied by a corresponding non malignant neoplastic condition of the leucoblastic portion of the bone marrow Such cases are, in fact examples of what might be termed non malignant erythroleukaemia. The very rare supervention in such cases of true myelosis (myeloid leukaemia) appears therefore to signify that the non malignant leucoblastic factor of the erythroleukaemic syndrome has taken on the malignant neoplastic character of full blown myeloid leukaemia whereas at first it corresponded to the (very rare) so called polymorphonuclear neutrophil variety or stage of myeloid leukaemia Why does the erythroblastic factor never manifest an analogous malignant transformation? [40] Recently the author visited in London with Dr Parkes Weber and he re emphasized the sometimes forgotten fact that polycythemia vera is nearly always characterized by hyperplasia of the myeloid as well as the erythroid elements of the bone marrow Because of this relationship it is difficult to gain information from the literature on the question of whether or not the incidence of leukemia is increased in those patients treated with radiation, venesection *or with drugs such as phenylhydrazine* and others Apparently this question cannot be answered since there are so few groups in which follow up has been adequate

and there are no large groups in which one form of therapy has been compared with another It can be stated however that we and others have often observed many patients with polycythemia vera who have had an associated leukemic blood picture prior to treatment of either condition [3, 4, 38, 40] For example Rosenthal and Bassen[41] have described a case in which active involvement of the bone marrow both myeloid and erythroid was found The patient presented a clinical and hematologic picture of polycythemia and leukemia and neither condition had been treated The tendency for patients with polycythemia vera to develop either a leukemia or an anemia in the spent phase of the disease has also been discussed by them Rosenthal and Erf[42] and Hirsch[43] have discussed the occurrence of osteosclerosis in patients having polycythemia vera of long duration The tendency toward high platelet counts is also emphasized[44] and the frequency of complicating thrombotic phenomena is pointed out by several observers[45-47]

Numerous observers have reported the association of polycythemia and lesions of the central nervous system in the region of the midbrain including tumors and Cushing's disease As an interne under Dr Harvey Cushing in Boston and later in the hospital at Yale University where Dr Cushing became Professor of History of Medicine after his retirement from Harvard the author saw and studied many patients with Cushing's disease or pituitary basophilism first described by Dr Cushing These patients frequently had high hematocrits and elevated red cell counts* In spite of the fact that there were many studies carried out by Dr Cushing then and by others later it is difficult to establish the fact that there is a true polycythemia with increased red cell volume in this condition The question of neurogenic polycythemia and polycythemia associated with various lesions in and around the pituitary and

* Dr Cushing reported this association in his book Papers Relating to the Pituitary Body Hypothalamus and Parasympathetic Nervous System (C C Thomas 1932 p 193)

midbrain have been discussed by Haynal and Graf [50] Carpenter and co workers[51] review the possible role of the hypophyseal hypothalamic system in the pathogenesis of polycythemia Moehlig and Bates[52] have partially reviewed the question of the influence of the pituitary gland on erythrocyte formation and report two interesting cases with an apparent definite polycythemia one with a combined basophilic and acidophilic adenoma of the pituitary and the other with a malignant angiomesothelioma of the adrenal In the former the bone marrow was not examined and in the latter the pituitary showed basophilic hyperplasia and the bone marrow was hyperplastic *They brought forth no clear cut evidence that in polycythemia vera there is derangement of this system* One can muster some evidence however for a relationship between the *hypophyseal hypothalamic system and polycythemia* since numerous observers including ourselves have observed polycythemia associated with Parkinson s disease and brain tumors, there is al o the possible polycythemia occurring in Cushing s disease Schulhof and Matthies[53] produced injury of the mid brain in rabbits and found that an increased red cell count de veloped suggesting again that the midbrain plays a role in the regulation of the number of circulating erythrocytes

The anemia of hypophysectomized animals can be repaired by injection of cobalt[54] [55] or by pituitary feeding[56] and ap parently this latter effect is not mediated through any of the other endocrine glands [57] Furthermore a sheep pituitary ex tract has been prepared by Ellis[58] and associates [59] which by subcutaneous injection (a) repairs the anemia of the newborn rat [60] [61] (b) repairs the anemia of hypophysectomy in the pres ence or absence of the pituitary target organs [62] (c) produces a polycythemia in the normal and hypophysectomized rat [57] [63] and (d) apparently is not identical with ACTH acting through the adrenals [57] [62] [63] This substance may possibly be a humoral substance[64] [65] [66] liberated within one hour after the onset of an anoxic stimulus [67] (See also discussion under SECONDARY

POLYCYTHEMIA Chapter III) Recently Contopoulos et al have extracted from the plasma of patients with polycythemia vera a humoral factor which when injected into rats stimulates red cell production and an increase in red cell volume Whether this factor is elaborated by the hypophysis is not known

Reznikoff and his associates[4] have observed in histological studies of the bone marrow that there are capillary thickening, and marked subintimal and adventitial fibrosis of the sub arteriolar capillaries arterioles and arteries They suggest that this may result in hypoxia of the blood forming tissues and thus lead to a polycythemia Also of interest here is the work of Schafer[45] Hypertension experimentally produced in dogs by surgical interruption of all the cervical afferent depressor path ways decreased following paravertebral sympathectomy as did the associated polycythemia Schafer theorizes that bone mar row anoxia or hypoxia results from vasoconstriction of the marrow arterioles which in turn stimulates red cell formation These investigations led him to do a sympathectomy in a young person suffering from polycythemia vera The operation resulted in a *temporary* fall in the number of red cells and also temporary relief of the patient s symptoms

Cases of polycythemia appearing in several members of a family have been reported[45] but this does not explain the nature of the process

Isaacs[69] studied a patient with polycythemia vera having a markedly elevated number of red cells and found that the blood viscosity as determined with an Ostwald viscometer was in creased to 11 times that of water He considers this to be about twice that of normal blood As has been observed by others,[70, 71] he found the uric acid to be elevated (6 9 mg /100 cc in a repeat study 8 9 mg /100 cc) in this same patient He comments also on the question of whether in polycythemia vera there is increased production or decreased destruction of red blood cells In his patient he found that the red cells were more resistant than normal to hypotonic salt solutions hemolysis

beginning at 0 3 per cent and reaching completion at 0 2 per cent This suggested decreased destruction of red cells as a cause of the increased number of red cells in his patient He also refers to the fact that in leukemia there may be an elevated uric acid content of the blood which has been attributed to the nuclear metabolites of the white cells but Schafer[49] also thought that the high uric acid in his patient with polycythemia vera might have been due to the 'discarded nuclei of the red cells Of interest in this connection is the view of Hickling[64] that high uric acid levels and gout are not frequently observed in the typical primary polycythemia or myeloid leukemia patient unless myeloid metaplasia is present

Isaacs[69] and Christian[7] have both noted that the reddish cyanotic appearance is apparently not always directly related to the increase in red cells In a case of an anerythremic erythremia described by Roger Morris[73] cyanosis was present but the red cell count was not elevated Christian[72] noted in a group of ten cases of polycythemia vera that the deep color was not always present Some patients appeared to be pale indicating that the depth of color in the skin is due in part at least to the location and state of distention of the capillaries[74] With reference to the cyanosis often observed several investigators have studied the capillaries the peripheral blood flow cardiac output and oxygen utilization in that disease In one patient with polycythemia vera Brooks[7] found that the cardiac output was only slightly increased and since the blood volume was markedly increased it seemed certain that the circulation rate was slow especially in the capillaries Blumgart and co workers[76] studied the velocity of blood flow and reported that it was decreased in two patients with polycythemia vera Altschule and co workers[77] found the cardiac output and cardiac work to be normal in three patients at rest but the capillary blood flow was slowed possibly due to increased viscosity It would seem that many of the symptoms and signs are due to a slowed capillary circulation of blood normally saturated with oxygen

Recently in Italy the author saw in consultation a patient with classical polycythemia vera who had previously been studied at the University of Milano by Professor L. Villa and I quote from the capillaroscopy reported by him on this patient

The first series of capillaries are very large, irregular, tortuous and thickly dilated, some of them being dilated markedly, and in these the stream of red corpuscles is made up of numerous erythrocytes which are almost stagnant, not moving at all, and one rarely sees a single erythrocyte proceeding at normal rate. In almost all of the arches the capillary circulation is slowed. Even in the successive orders of capillaries which are scarcely evident in the region of the arch there is noted irregularity of the capillaries with marked dilatation. On the whole the capillaries are irregular as to course and dilatation, *especially in the capillary arch, with marked slowing of the circulation* of the erythrocytes.

The diagnosis depends on the total clinical picture. A markedly elevated red cell count without obvious cause must be present, concurrent with a normal or near normal arterial blood oxygen saturation and an increased total red cell volume. An increased blood *volume per se does not*, as inferred by Haden,[2] permit one to differentiate polycythemia vera from the secondary polycythemias such as those associated with congenital heart disease or pulmonary disease. This point is brought out in an article by Schafer[49] and has been shown in our studies.

Incidence and Prognosis

The incidence of polycythemia vera is low, but accurate information on this point is not available. It is, however, less than that of leukemia. One recently conducted study indicates that more than 10 000 persons in the United States die of leukemia each year.[78] Likewise, there is little information available on the prognosis after treatment. There have been several cases reported to have lived 10 years or more,[3, 4, 8, 43, 60] *but there are not many reports in which adequate follow-ups* or analyses of end results in large groups of patients are given

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varies from several months to many years In the true form of polycythemia the usual duration even after diagnosis which is usually not established for over a year is a number of years [8]

Therapy

Before we introduced P³² for the treatment of this condition [83] therapy had usually been periodic venesections [84, 85] destruction of excess red cells by such agents as phenylhydrazine [6, 88] or inhibition of red cell production by Roentgen irradiation to the spleen long bones or whole body Recently nitrogen mustards and other agents have been introduced and the details of the treatment of ten cases are reported but again there are no long term observations [89] It is difficult to evaluate the comparative end results of any of these forms of therapy since there has been no large group treated by one method which has been followed long enough to determine the length of remission produced and the average length of life after onset or after beginning of treatment A questionably effective method has been the use of a diet low in iron Recently several authors have advocated the use of such a diet in conjunction with either venesections or radioactive phosphorus [90, 91] although none advocated it as the sole method of therapy In one patient Rosengart[95] found the low iron diet to be ineffective It seems very probable that an iron deficient diet carried on for long periods of time might lead to the situation often observed in patients treated solely by venesection The red cell count and total red cell volume remain high but the hemoglobin falls to abnormally low levels making it unwise further to deplete the patient of iron In this connection it should be mentioned that a very low animal protein diet has been found quite effective in reducing the red cell count and hemoglobin in a significantly large number of cases [96, 97] This diet also may be poor in iron but is certainly a deficient diet and for this reason is to be avoided Daraprim an antimalarial drug which has antifolic

Tinney et al[38] reported that at least 36 patients out of 163 lived more than five years after onset. Videback[8] in the study of 125 patients with polycythemia treated by drugs, venesection or x ray, reported that the average duration of life after onset was only about seven years for the group that could be observed for 20 years or longer. In a group of 64 patients who could have been observed for at least ten years, the average duration of life was again about seven years. Therefore polycythemia vera is ordinarily not a benign lesion since at the age of 52 the normal life expectancy would be over 20 years. In another group the median survival time after first treatment in 28 patients treated by spray x irradiation was approximately 6.6 years (calculated from the data of Richardson and Robbins).[7] Since their patients had an average age of 54 at first treatment, it is probable that the median survival from onset of the disease may be up to two years longer, giving these patients a median survival of 7–8 years.[7] The above three series of patients were treated by Roentgen rays and/or venesections and/or phenylhydrazine.[8, 38]

It has been stated that this condition is benign[8] in spite of the fact that no large group *of patients adequately followed* have been shown to survive more than six to eight years after onset. There have been scattered reports of individual cases treated with various forms of therapy used in the past surviving as long as 15 or 20 years. However, the natural course of the *untreated case is really not known*, although it seems *clear that* if a large series were followed to death and not treated, the death rate from hemorrhage and thromboses would be extremely high, the average life duration would be much under six years, and one would not classify the condition as benign.

In general the disease has in the past been recognized as one with a fatal prognosis and one in which thromboses are common[44, 45, 46, 81] so that life expectancy has been considered poor. Lee stated, "The prognosis is inevitably *fatal but it must be* remembered that this is a chronic disease, the duration of which

seen in this disease and was unrelated to the degree of athero sclerosis One of our patients on whom autopsy records are available died at the age of 49 of an acute coronary thrombosis which had occurred 13 days earlier In this case coronary atherosclerosis was present

Previously[111] we have reported four cases of polycythemia associated with multiple myeloma These added to the at least three previously reported cases make seven with this association[112, 114] Videbaek[8] has observed three cases of hypernephroma in a group of 125 cases of polycythemia vera and Forssell[115] reported one other case with this association The present author has observed two cases of hypernephroma in association with polycythemia vera The relationship of the two conditions is not clear

Newer Studies

Clinical physiologic metabolic and therapeutic studies on 303 patients have been carried on by the author and his associates during the past 20 years all directed toward a better understanding and treatment of this condition At the beginning of the work it was realized that since the condition was relatively rare and since there was no study on a large group *of patients detailed comprehensive and broad studies with* complete follow up should be carried out Should it turn out that twenty years later a large number of cases might have been observed and treated Such a large experience has eventuated and such detailed studies now seem worth recording for the use of those who study and treat polycythemia more rarely *

Our experiences are with patients definitely having polycythemia vera those having a relative polycythemia of un

In this work the author has had for short or longer periods of time the collaboration and association of many young physicians working with him in the laboratory and the findings reported here have in most cases been previously reported with these collaborators in the medical literature which is referred to

and antifolinic acid properties, has recently been tried in polycythemia vera, but it is too early to assess its value [05, 06]

Pathology

In the literature we have been unable to find a comprehensive report on the pathology of polycythemia vera based on the study of a large number of patients The relative rarity of the disease makes it difficult for any one individual or group to carry out such a study The best general statements, however (number of patients and blood status at the time of death not stated) are those of Zadek [98] Gaisbock [19] and Sternberg [99] The significant findings at autopsy were changes in the bone marrow splenomegaly and because of the large blood volume plethora of all the tissues

In a careful review of the literature only isolated case reports describing the bone marrow were found A number of authors (Moewes [100] Glaessner [101] Loew and Popper [10] Schneider [103] Luce [104] Hutchinson and Miller [105] Hamilton and Morse [106] and Bishop[107]) found replacement of the adipose tissue of the femoral marrow by blood forming tissue by gross and microscopic observations on single cases Of the other bones studied only the tibia (Watson Wemyss[108]) and the humerus (Luce[104]) were specifically mentioned as containing hematopoietic marrow Some authors (Weber and Watson[109]) state that these findings occur in all the long bones

Miller[110] reported five cases of polycythemia vera in which postmortem examination disclosed myocardial infarction Three had coronary occlusions and although thrombi could not be demonstrated in the other two the myocardial damage resembled that usually associated with coronary artery occlusion Studies of the coronary vessels showed that in four of these five cases there was little or no atherosclerosis or if present it was to a lesser degree than would be anticipated on the basis of the age of the patients It was thought that the coronary thromboses represented a manifestation of the thrombotic tendency

Finally in the group having *secondary polycythemia* there was on clinical and laboratory examination clear evidence of cardiac pulmonary or other abnormality which could be etiologically related to the polycythemia or there was a history of residence at high altitude for relatively long periods of time Tabulation of the clinical and laboratory findings in these three groups will be given in tables and graphs

History

Seven per cent of the patients with polycythemia vera had a family history of polycythemia leukemia or pernicious anemia [68] In one family there was a physician with polycythemia vera who had a sister and a niece with polycythemia vera and another sister with chronic myelogenous leukemia The father of one patient had died of polycythemia vera and the brother sister and father of three others had pernicious anemia In three others near relatives had leukemia The familial incidence therefore is low and its significance is not clear although this question has been discussed by several authors [8] In the group with relative polycythemia there was no history of familial or other related disease and this was also true of those with polycythemia secondary to cardiac or pulmonary disease

Seven per cent of the patients with polycythemia vera had had malaria A history of exposure to fumes from oil gas or paint was found in 6 per cent One patient had been exposed to dust containing silica In these patients there was no evidence of pulmonary physiological impairment At the time of our first examination 6 per cent were living or had lived at an altitude of 5 000 feet or higher With reference to residence at high altitude as a possible etiologic factor during two expeditions to the Peruvian Andes [22, 118] we failed to find one patient with polycythemia vera listed in the records of the Cerro de Pasco Mining Corporation Hospital at La Oroya Peru For many years this hospital has served a large population of people living

known etiology (perhaps many of those formerly called Gaisbock polycythemia)[116] and those who have a polycythemia clearly secondary to some other condition such as pulmonary or heart disease or residence at high altitudes[2] Except for a few patients with heart or pulmonary conditions and the subjects with altitude polycythemia most of these patients were referred to us with the probable diagnosis of polycythemia vera Hence the whole group does not give a true picture of the proportional incidence of the various types of polycythemia

Clinical Findings

There are 231 patients with polycythemia vera * To qualify for this classification the patient must have had an unexplained elevation of the red cell count to 7 000 000 or higher when first observed by us or there must have been definite evidence of this degree of elevation in the past A combination of a definitely enlarged spleen with moderate or great elevation of the red cell count was considered diagnostic of the disease Associated elevation in the numbers of platelets and white cells was considered as supporting evidence for the existence of polycythemia vera if the elevation in the number of red cells was insufficient to establish the diagnosis

A second group consisting of 31 patients had relative polycythemia In this group on the average somewhat younger than the polycythemia vera patient there was often a mild elevation in the number of red cells to perhaps 6 000 000 or 6 500 000 without a palpably enlarged spleen and without elevation in the number of platelets or white cells In these individuals there was a decrease in the plasma volume and no true increase in the total red cell volume[116] Thus their high values for red cell counts were misleading No true polycythemia was present

* Much of this discussion is concerned with the 109 patients on whom complete data were available at the time writing of the book was begun

of the patients complained of chest pain usually brought on by exertion The pain varied from heartburn to an atypical angina in a fifth of these patients In the others the pain was not characteristic of any particular symptom complex The eighth most common symptom was pruritus It often occurs after exercise or a hot bath Itching is a relatively common symptom and an especially distressing one in patients with polycythemia vera particularly in those patients who have an elevated red cell volume *Often it is relieved after the red cell volume re*turns to normal but this is not true of all patients and many of them continue to have this symptom even though they are *in* otherwise good condition In some of these patients there was an atypical dermatitis which was unclassifiable by the dermatologist In a few there were maculopapular skin lesions which cleared with therapy In rare cases we found the itching associated with an allergy to some food and the *symptom improved after elimination of that particular food* or after the use of antihistaminics The fifth most common symptom was some form of abdominal pain varying from chronic indigestion to epigastric pain This was a prominent complaint in 26 per cent of the patients Of these 48 per cent *(20 patients) had peptic ulcers In two cases these could not be* demonstrated by x ray examination although the histories were clearly those of peptic ulcer For those cases in which the histories gave the site of the ulcer the ulcers were duodenal *in* about 90 per cent and gastric in 10 per cent There were 14 per cent having arthritic complaints and in an additional 7 per cent there was a definite history of pains in the extremities A definite diagnosis of rheumatoid arthritis had been made in 5 of the 159 cases hypertrophic or osteoarthritis in 6 cases and *gout in* 13 cases (uric acid ranging from 5 6 to 11 7) Four per cent had a history of thromboses other than cerebral or coronary At least three of the patients had very extensive thromboses with onset before we saw them One was a portal thrombosis and the other *multiple thromboses of the arm and another mesenteric*

at altitudes of from 12,000 to 17,000 feet Other studies reported below add further evidence for the view that anoxia or hypoxia in the ordinary sense is not etiologically related to polycythemia vera

Symptoms and Signs

The symptoms and signs listed in decreasing order of incidence are ruddy cyanosis 62 per cent headache, 45 per cent, dyspnea or orthopnea 34 per cent dizziness or vertigo, 28 per cent eye complaints 27 per cent epigastric discomfort 26 per cent precordial pain 16 per cent pruritus, 14 per cent a definite history or diagnosis of peptic ulcer 13 per cent, thrombophlebitis of the leg or arm 13 per cent cerebral thrombosis, 10 per cent gout 7 per cent coronary thrombosis, 4 per cent, thromboses other than cerebral or coronary, 4 per cent neoplasms 4 per cent

Headache varied in severity from mild and infrequent to intermittent and severe and in location from frontal to occipital Many of these patient have occipital headaches radiating down the neck Some patients described headaches on awakening The next most common symptom was dyspnea or orthopnea Of the patients with this symptom, 97 per cent had exertional dyspnea and 9 per cent a mild orthopnea In most instances the exertional dyspnea was mild to moderate In a few both exertional dyspnea and nocturnal orthopnea were present There seems to be an increased incidence of coronary occlusion among patients with polycythemia vera Four per cent of our patients had had a myocardial infarction As noted above Miller[110] concluded that the complicating coronary thrombosis was usually associated with little or no coronary arteriosclerosis Pierce and Gofman[118] studied the serum cholesterol and lipoproteins in 10 of the patients reported here and found no pattern specifically abnormal The next most common symptoms was dizziness varying from rare to frequent episodes The eye complaints consisted primarily of scotomata Sixteen per cent

stomach complaints 35 per cent had vertigo 7 per cent had dyspnea Thus symptoms are sometimes observed in the presence of normal red cell counts However, this group is small and total red cell volume determinations were not done on all of this group Even in the presence of relatively normal red cell counts some may have had increased total red cell volumes (See further discussion of blood volume below)

Age, Sex Race and Geography

Figure 1 gives the distribution of age at onset of this group of patients with polycythemia vera It shows that the first symptoms usually occur when the patient is between 50 and 60 years of age There are a few cases under 30 the youngest being 18 years and one over 80 years of age When the age of onset is compared with the age distribution of the general population it is seen that although the age of onset is predominantly in the

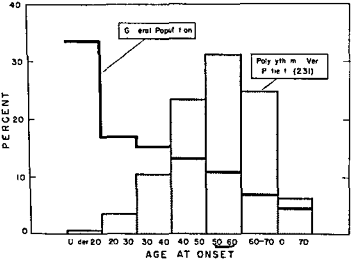


Fig 1 —Age of onset for polycythemia vera patients contrasted with the distribution of age groups in the general population

Had the polycythemia been discovered and controlled earlier in the course of the disease these complications might have been prevented, since in our treated patients (see below) the incidence of thromboses has been markedly decreased This has been an important factor in life extension With reference to the problem of gastric hemorrhage in cases of polycythemia vera, four patients (2 5 per cent) had a history of gastric hemorrhage before we saw them In one there had been definite roentgenological evidence of a hiatal hernia and a duodenal diverticulum one had a duodenal ulcer, one had gastritis, and one had no evidence of an ulcer by x ray examination Ten patients had a history of one or more attacks of epistaxis, and in one each unexplained bleeding from the lungs or uterus A hysterectomy was performed in the latter case

It should be emphasized that the symptoms of this syndrome are varied and may be referred to practically any system of the body On this account many of these patient had been thought to be suffering from nervous exhaustion or neurasthenia and the true diagnosis was not made for several years Fatigue of some degree is a very common symptom No attempt has been made to list its incidence here because of the obvious difficulty of evaluating such a symptom Even though their red cell counts were markedly elevated a few patients (less than 10 per cent) were free of the principal symptoms mentioned except for mild fatigability and their polycythemia was discovered more or less accidentally or during a routine physical examination

In summary the typical patient with polycythemia vera has a history of headache nervousness scotomata, ruddiness of the face and mucous membranes fatigue after moderate exertion and he may have had one or more thromboses in the arteries or veins

Fourteen patients had red cell counts under 5 5 million at the time of the initial physical examination by us The symptoms were as follows 62 per cent had ruddy cyanosis 57 per cent had headaches 42 per cent had eye complaints 35 per cent had

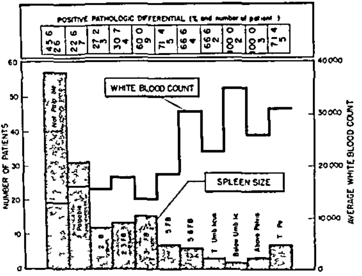


FIG 2 —The relationship between size of the spleen white cell count and pathologic white cells in the blood

Figure 2 shows the variability in size of the spleen In the majority of patients the spleen was either not palpable or just palpable at the costal margin There is a definite tendency however for larger spleens to exist although those being enlarged to below the umbilicus and into the pelvis are present in only a small number of patients It is important to remember that 90 per cent of these patients were in hematological relapse with elevated red cell counts when first seen by us Of those with palpable spleens 93 per cent were in relapse whereas in those who did not have palpable spleens only 84 per cent were in relapse Of interest in this connection is a study of 17 patients with polycythemia vera who did not have palpable spleens By x ray examination 41 per cent of these patients had enlargement of the spleen This verifies the fact that by percussion and palpation it is not always possible to detect splenic enlargement However it should also be pointed out that in the author s

50 to 60 year age group the incidence is greatest in the 60 to 70 year age group Age of onset is usually taken as the date the diagnosis was first made, but in some cases the age of onset has been taken as that date on which a disinterested observer found definite evidence of the disease to be present from the history, physical and laboratory data In any event the average age of onset in our group, 52 is in agreement with that found in other groups [8] Since the onset of this disease is insidious the figure of 52 years probably represents the maximum age of onset In many patients a history of headaches, ruddy complexion bloodshot eyes, and even a left upper quadrant mass of months or even years' duration may be elicited

Fifty seven per cent of the patients were male and 43 per cent were female The sex incidence ratio is 1 30, This is like that observed in chronic myelogenous leukemia [119] There is no preponderance of any particular nationality or geographic or religious group in this series unlike that reported by Reznikoff who analyzed the records of six hospitals having a low incidence of eastern European Jews in general admission (average of less than 10 per cent) and found that 48 per cent of 134 cases of definite polycythemia vera recorded were from this particular ethnic group [48]

Physical Findings

Ruddy cyanosis of the face fingertips nose ears lips or mucous membranes of the mouth and pharynx was observed in 62 per cent of our patients This cyanosis had a deep reddish tinge unlike the blue cyanosis seen in secondary polycythemia

Clubbing of the fingers often seen in other forms of polycythemia [22] was not present in these patients with polycythemia vera Often there was engorgement of the retinal vessels but no choking

Three patients were observed to have associated Parkinson's disease The relationship of the midbrain hypothalamus and pituitary to polycythemia has been discussed earlier

discussed by numerous authors[15] We have observed this in at least three of our patients but not in patients who are under adequate control with radioactive phosphorus It seems certain *that the slight enlargement of the liver so often observed is on* the basis of increased blood volume and consequent distention of the vascular bed of the liver and not cirrhosis

For purposes of discussion of the blood pressure the patients having a systolic pressure greater than 150 and/or a diastolic pressure greater than 90 are classed as hypertensive So judged 50 per cent of the patients were hypertensive and 50 per cent were normotensive In Figure 4 is presented the distribution of the systolic and diastolic pressures of these patients It is seen that there is a definite tendency toward elevation of the blood pressure Figure 5 shows there is no correlation between systolic

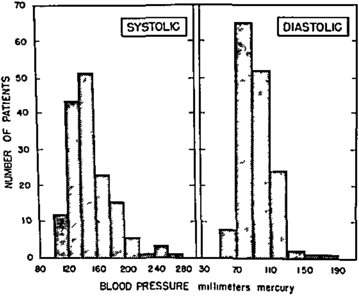


FIG 4 —The distribution of the systolic and diastolic pressures in polycythemia vera patients

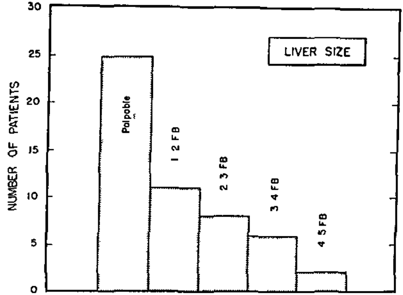


FIG 3 —The variability in the size of the liver in polycythemia vera patients

experience the radiologist may fail to report an enlarged spleen when the clinician can palpate it easily Sometimes it is difficult to decide by palpation whether the enlargement is due to spleen or kidney In this case x ray studies and even pyelography may be necessary This is extremely important since a renal neoplasm may be removed surgically and in rare instances removal of such a renal neoplasm will relieve the polycythemia The mechanism of such relief is not understood Figure 2 also shows a direct correlation between elevation in the number of white cells the presence of pathologic white cells * and splenomegaly

The liver was palpably enlarged in 33 per cent of the patients However as Figure 3 shows when the liver is enlarged it is usually only barely palpable or 1 to 2 fingerbreadths below the costal margin The not uncommon association of hepatomegaly and/or cirrhosis of the liver with polycythemia vera has been

* Metamyelocytes myelocytes or myeloblasts

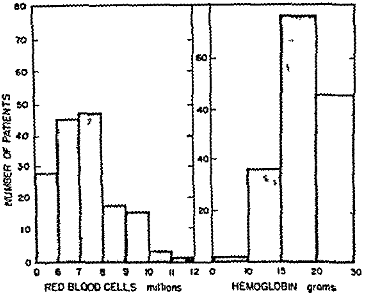


FIG 6—The red cell count and hemoglobin in polycythemia vera patients at the time of initial examination

therapeutic response Figure 6 also shows the distribution of hemoglobin values It is seen that the largest group of patients had a hemoglobin concentration between 15 and 20 Gm /100 cc although there was a sizable group with a hemoglobin concentration over 20 Gm /100 cc Here again just as in the case of the red cells many of those patients who were in the lower range had had previous specific therapy or venesections

The average mean corpuscular hemoglobin was 24 9 Gm the average mean corpuscular hemoglobin concentration 29 Gm / 100 cc of packed cells These are slightly below the range of normal indicating that these cells are hypochromic This probably represents the effect of venesections carried out on many of these individuals prior to our seeing them Perhaps they also fit the concept that certain of the polycythemic red cells are abnormal [222] This will be discussed later under red cell life The

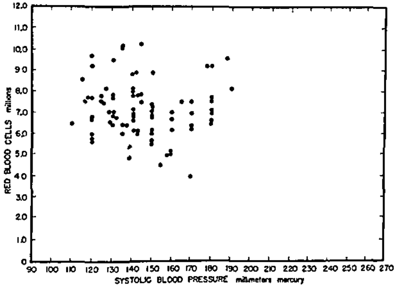


Fig 5 —The systolic pressure as a function of the red cell count in polycythemia vera

pressure and the red cell count the scattering of points being almost random in distribution A similar study of diastolic pressure also showed no correlation with the red cell count However these results do not prove that there is no relationship between total red cell count and red cell volume and the presence of hypertension in polycythemia vera [120] This will be discussed in more detail below

Laboratory Findings

Figure 6 presents the distribution of the number of red cells at our initial examination The largest group had values between 7 and 8 million although a large number were in the 6 to 7 million range Of those with values below 6 million 86 per cent had had therapy during the previous six months with phenylhydrazine, P^{32}, x ray venesection or had had gastro intestinal or other bleeding of sufficient magnitude to produce a

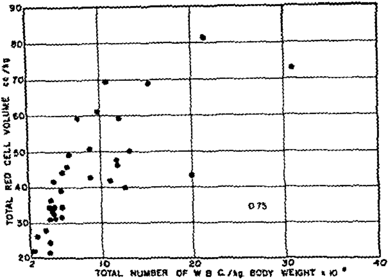


Fig. 8.—The total number of white cells/kg of body weight and the total red cell volume showing that there is a direct correlation between increase in red cells and white cells in polycythemia vera [7]

In 35 unselected patients[17] the *coefficient of correlation* between the total number of circulating white cells and red cells was 0.75 (Fig. 8). Thus usually when there is an elevated red cell count there is a proportional increase in white cells and platelets or a total hyperplasia of the hematopoietic tissue not an increase in red cell formation alone. This has not been sufficiently emphasized in previous writings. Dr F Parkes Weber of London, who has studied polycythemia for over 65 years, recently told the author: "Investigators have generally failed to realize that polycythemia vera is a condition involving not only the red cells since the white cells and megakaryocytes are usually increased to an even greater degree than the red cells."

In a group of 159 patients with polycythemia vera immature cells of the myeloid series, metamyelocyte to myeloblast, were observed in the peripheral blood of 111 when first seen by us

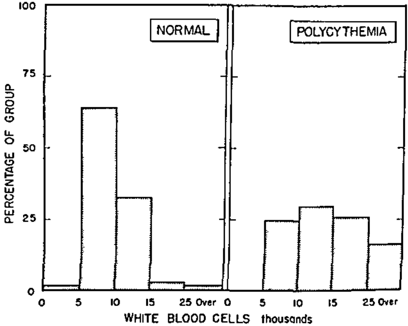


FIG 7—The white cell count in polycythemia vera patients and in 200 normals

average mean corpuscular volume 85 cμ is approximately normal

Figure 7 shows that there is a distinct difference in the incidence of elevated white cell counts in patients with polycythemia vera as compared with 200 normal persons Twenty eight per cent of normal individuals had white cell counts between 10 000 and 15 000 with only a few having values above this range In polycythemia vera 74 per cent of the group had white cell counts over 10 000 with 5 per cent over 50 000 Of the 40 patients who had white cell counts under 10 000 most had had previous therapy—ten with P[32] x ray or radium in sufficient quantities to influence the white cell count and most of the others with phenylhydrazine or phlebotomy It is not known whether phlebotomy will affect the white cell count, although a leukocytosis may result from phenylhydrazine

(Fig 9) Over 65 per cent had platelet counts over 300 000 some ranging from 500 000 to 1 400 000 Again recent therapy modified the platelet counts in many of these patients so that this figure would be higher in untreated patients

A marked and persistent hypochromia associated with high red white and platelet counts was a common finding in patients who had been treated by frequent venesection before we saw them Figures 10A (A F) and 10B (K J) show the gradual correction of iron deficiency as well as the control of platelet and white counts when marrow inhibition therapy is substituted for repeated bleedings

Patient A F (Fig 10A) a 66-year-old white woman was first seen in October 1947 She had been treated by venesection since the diagnosis of polycythemia vera in 1942 at almost monthly intervals in the six months preceding her first visit here As can be seen in the figure her first hemogram showed high platelet and white cell counts high normal red count and low hemoglobin Hypochromia could be observed for some time after the cessation of venesection and institution of P^{32} therapy reaching a normal pattern toward the end of the second year

Patient K J (Fig 10B) a 51 year old white woman was first seen in November 1949 A diagnosis of polycythemia vera had been made two years

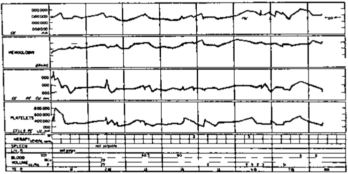


FIG 10A —Patient A F an example of hypochromia associated with high red white and platelet counts as a result of treatment with venesection only With institution of P^{32} therapy and discontinuation of venesection all the values begin to assume a more normal picture

In addition, in 13 of these 111, nucleated red cells were observed and in 11 patients ranged between 1 and 10 per 100 white blood cells in 1 patient 22/100 WBC, and 1 patient 88/100 WBC The latter patient had had a splenectomy Of the 111 having immature white cells of the myeloid series in 49 the most immature white cell was the metamyelocyte, in 48 the myelocyte in 8 the promyelocyte and in 6 the myeloblast Forty eight had no abnormal cells Although it may be thought that in some patients the incidence or the appearance of immature cells of the myeloid series in the peripheral blood may be related to extramedullary hematopoiesis our in vivo studies of iron metabolism indicate that although it occurs, extramedullary hematopoiesis in the spleen and/or liver is not common in polycythemia vera [1, 13]

The platelet counts are usually elevated in these patients

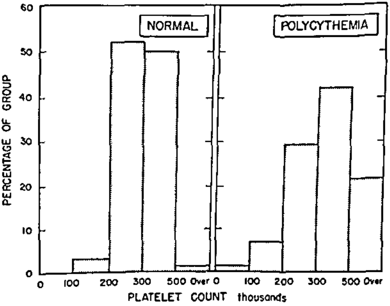


FIG 9—The platelet counts in patients with polycythemia vera compared with normal.

A/G ratio averaged 1 24 in 37 patients with a range from 0 6 to 2 8 In 19 patients the serum bilirubin averaged 0 93 mg per cent and ranged from 0 05 to 3 0 In 47 patients the uric acid averaged 6 6 mg per cent ranging from 2 8 to 11 7 mg per cent (see discussion of gout) In 10 patients the fecal urobilinogen (three day stool sample) averaged 212 mg over a 24 hour period and ranged from 28 to 586 mg per day In 71 patients the arm to tongue circulation time (Decholin) averaged 17 4 seconds with a range of 8 to 30 seconds This is increased and probably is due to the effects of an increase in viscosity and in blood volume All of the patients discussed in this paragraph were in hematological relapse at the time these tests were made

In an unselected group of 97 patients (95 per cent having a red cell count over 5 5 million) some abnormality was found in the urine in 71 Sixty per cent of these patients had pathological urines as exhibited by quantities of albumin ranging from a trace to 35 mg /100 cc 53 per cent had occasional up to 50 red blood cells per high powered field 34 per cent had anywhere from occasional to large numbers of white blood cells per high powered field and 30 per cent had occasional casts either fine or coarse and granular We associate these changes with varying degrees of nephrosclerosis which is often found in this age group and especially in patients with polycythemia vera At autopsy it is not unusual to find pathologic changes particularly nephrosclerosis in the kidney (Table 3) The exact relationship between kidney changes to polycythemia is not clear but we have observed on numerous occasions improvement in the urinary findings after the red cells have been brought to normal by therapy In a few instances the urine has become completely normal when the hematological picture returned to normal For example in the case of one patient who had a red cell volume over twice normal (68 5 cc /Kg of body weight) and a decreased plasma volume (24 7 cc /Kg) the initial urinalysis showed 4+ albumin 10–15 white cells/high powered field and 20–25 red cells/high powered field Six months later and following a course

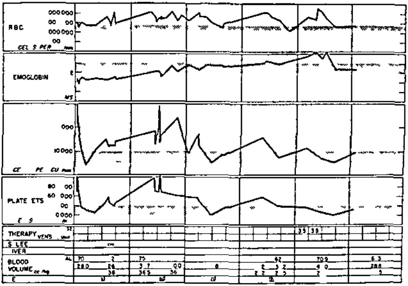


FIG 10B —Patient K J another example of a patient with marked hypochromia due to treatment with venesection which improves with P^{32} therapy

earlier when her red count was reported to be 8 5 million She was treated by a total of 35 r anteriorly and 35 r posterior body bath x ray therapy with a reduction in the red count to 6 million Her count rose again immediately however and she was treated by venesection alone between February 1948 and November 1949 (twenty four 500-cc venesections) Her initial hemogram was similar to that of the preceding case with an excessive platelet count high white count high normal red count and low hemoglobin Her total red cell volume was within normal limits Recovery from the iron deficiency was somewhat slower than in the preceding case however possibly as a result of a period of vaginal bleeding in early 1950 Iron turnover studies with Fe^{59} in April 1950 showed a very rapid disappearance of tracer iron from the plasma but relatively low plasma iron in agreement with the hypochromia found The patient received no further venesections and with the institution of P^{32} therapy the hypochromia could be seen to improve gradually until a normal pattern of values could be observed a year later

The NPN in 26 patients averaged 45 mg per cent with a range of 26 to 66 mg per cent The total proteins averaged 7 6 Gm per cent with a range of 5 7 to 10 1 in 38 patients The

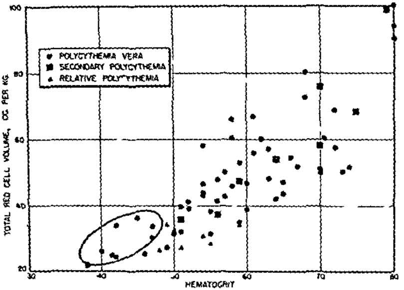


FIG 11 The total red cell volume plotted against the hematocrit showing the great variation in red cell mass for a given hematocrit

from secondary polycythemia by measurement of the blood volume (see Chapter III SECONDARY POLYCYTHEMIA)

Bone Marrow

A previous study[30] analyzes bone marrow differentials before during and after treatment with P[32] (Table 1) In comparison with the normal it is seen that there is a distinct increase in the number of nucleated red cells in the bone marrow in polycythemia vera which is in general agreement with the findings of Manning [?] However the increase is not sufficient to be diagnostic and does not permit differentiation of polycythemia vera from secondary polycythemia As in the case of leukemia[30] periodic punctures during therapy are not of much value in assessing or regulating therapy There is need for more marrow biopsy data from many parts of the marrow since in polycythemia vera there is probably a change from fatty

of P[3] his red cell volume was within normal range (31 6 cc /Kg) and the urinalysis showed no albumin 1–2 white cells and no red cells The probable slowed blood flow in the cortical arterioles may be the cause of the kidney change In individual *instances there may have been other causes such as hemorrhage* or infection

Blood Volume

In a previous report from this laboratory the literature was reviewed and the findings in 53 patients analyzed[1 1 4] as follows The patients were divided into three groups on the basis of the hematocrit Group I comprised 32 patients with a hematocrit of 55 or greater Of this group 30 had elevated total red cell volumes ranging from 38 8 to 93 9 cc Kg of body weight The other two patients had total red cell volumes of 31 3 and 34 9 cc Kg of body weight Twenty two of the 32 patients had plasma volumes that were below the lower limit of normal Of the remaining ten eight had plasma volumes below the average and two were above average but within the range of normal Group II comprised nine patients with hematocrits from 50 to 54 Seven had elevated total red cell volumes In this group only three patients had low plasma volumes five had normal plasma volumes and one was above normal In Group III those with hematocrits below 50 the total red cell volume was normal in ten and low in two The plasma volume was in the normal range in eight patients low in three and elevated in one The only reliable measure of red cell in the individual patient is the total red cell volume not the red cell count hemoglobin or hematocrit because of the variation in plasma volume (Fig 11)

The elevated blood volume in polycythemia vera in relapse is then due exclusively to an increase in total red cell volume However the blood volume is not increased proportionally to the increase in red cell volume since the plasma volume is generally decreased Polycythemia vera cannot be differentiated

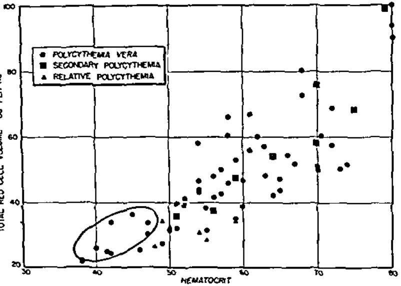


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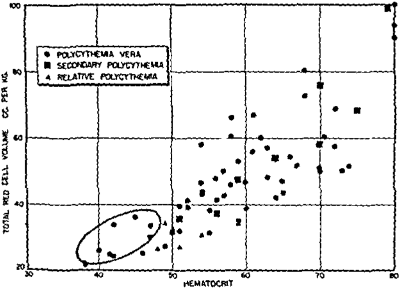


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TABLE 1 —*Bone Marrow Findings in Polycythemia Vera Patients as Compared with Normal Values*

	Normal	Pretreatment		Post-treatment					
				1-3 months (4 cases)		4-9 months (5 cases)		In excess of 9 months (16 cases)	
	Average (20 cases)	Average (18 cases)	Range	Average	Range	Average	Range	Average	Range
Segmented	19.6	16.7	6.6–25.0	16.7	7.8–23.6	16.3	6.6–23.0	16.3	5.0–36.4
Band cells	24.3	13.7	5.0–22.0	15.5	8.4–21.6	12.8	5.0–18.0	15.4	11.0–22.4
Myelocytes	20.8	18.4	9.8–32.2	19.5	12.0–27.0	18.0	9.8–25.8	23.4	14.6–41.0
Eos. myelocytes	1.6	1.0	0.0–2.6	0.7	0.2–1.8	0.3	0.2–0.4	1.6	0.0–5.0
Bas. myelocytes	0.04	0.3	0.0–0.8	0.3	0.0–0.4	0.2	0.0–0.6	0.2	0.0–1.0
Progranulocytes		2.1	0.0–11.4	3.4	0.0–9.6	6.2	0.0–11.4	2.2	0.0–6.0
Myeloblasts	2.2	1.0	0.2–2.8	0.8	0.4–1.4	1.2	0.6–2.8	0.9	0.3–5.0
Eosinophils	0.8	1.7	0.6–4.0	1.4	1.0–2.2	1.5	0.8–2.2	1.8	0.6–4.4
Basophils	0.02	0.4	0.0–1.0	0.1	0.0–0.4	0.5	0.0–1.0	0.4	0.0–1.0
Lymphocytes	11.7	3.6	0.5–8.7	6.[illegible]	2.4–16.5	3.2	1.4–5.4	3.2	0.6–5.8
Monocytes	0.4	0.4	0.0–1.6	0.4	0.2–0.6	0.2	0.0–0.8	0.1	0.2–1.0
Normoblasts	15.0	33.1	22.4–53.2	27.2	24.2–44.0	33.0	23.8–53.2	28.9	10.0–59.6
Erythroblasts	1.7	4.9	1.8–13.0	3.1	0.2–8.6	6.2	2.8–14.0	3.0	1.2–5.0
Megaloblasts	0.2	1.5	0.0–3.4	2.6	0.0–4.8		1.0–3.2	1.3	0.2–3.2
Plasma Cells		0.5	0.0–2.0			0.5	0.0–1.8	0.3	0.2–1.8
Megakaryocytes				0.8	0.0–0.8	0.1	0.0–0.4	0.3	0.2–1.0

marrow to red marrow involving both the red and white cell precursors. The ideal method for the study of the bone marrow in this condition is by histological section after biopsy or bone marrow punch. Block, Jacobson, and Bethard[114, 115] have found that in about 80–85 per cent of the cases of polycythemia vera, sections of the marrow from the sternum were diagnostic of the disease even though the patient had normal or subnormal hemoglobin values as a result of hemorrhage, phlebotomy, or treatment with phenylhydrazine and could be differentiated from cases of secondary polycythemia. These authors described the marrow as being hyperplastic with a replacement of much of the adipose tissue by hematopoietic tissue. There was a hyperplasia of cells of the megakaryocytic, erythroid, and myeloid series and a tendency for cells of the erythroblastic series to occur in small clusters. They found that following treatment with P^{32} the marrow was uniformly converted to a normal cellularity or slight hypocellularity; however, a slightly increased percentage of normoblasts remained. Berlin in this laboratory studied 21 cases by the punch needle biopsy technique and found histological changes in agreement with those of Block and co-workers.[114, 115] After P^{32} the effect was a reduction in the total volume of hematopoietic tissue with a reversion of the marrow to a normal or almost normal architecture. Thus sternal marrow puncture is of limited value but bone marrow sections are of great value in diagnosis and in assessing therapy.

Viscosity

The viscosity was determined in an Ostwald viscosimeter and compared to water at the same temperature. Figure 12 shows the viscosity of the blood as a function of the red cell count in millions. The coefficient of correlation between the viscosity and the red cell count is 0.55, which is significant. This may be of considerable importance in the pathogenesis of the thromboses and hemorrhages seen in this syndrome.

TABLE 1 —*Bone Marrow Findings in Polycythemia Vera Patients as Compared with Normal Values*

	Normal	Pretreatment		Posttreatment					
				1-3 months (4 [illegible])		4-9 months (5 [illegible])		[illegible] 19 months (16 [illegible])	
	Average (20 [illegible])	Average (18 [illegible])	Range	Average	Range	Average	Range	Average	Range
Segmented	19.6	16.7	6.6-25.0	16.7	7.8-23.6	16.3	6.6-23.0	16.3	5.0-36.4
Band cells	24.3	13.7	5.0-22.0	15.5	8.4-21.6	12.8	5.0-18.0	15.4	11.0-22.4
Myelocytes	20.8	18.4	9.8-32.2	19.5	12.0-27.0	18.0	9.8-25.8	23.4	14.6-41.0
Eos. myelocytes	1.6	1.0	0.0-2.6	0.7	0.2-1.8	0.3	0.2-0.4	1.6	0.0-5.0
Bas. myelocytes	0.04	0.3	0.0-0.8	0.3	0.0-0.4	0.2	0.0-0.6	0.2	0.0-1.0
Progranulocytes		2.1	0.0-11.4	3.4	0.0-9.6	6.2	0.0-11.4	2.2	0.0-6.0
Myeloblasts	2.2	1.0	0.2-2.8	0.8	0.4-1.4	1.2	0.6-2.8	0.9	0.3-5.0
Eosinophils	0.8	1.7	0.6-4.0	1.4	1.0-2.2	1.5	0.8-2.2	1.8	0.6-4.4
Basophils	0.02	0.4	0.0-1.0	0.1	0.0-0.4	0.5	0.0-1.0	0.4	0.0-1.0
Lymphocytes	11.7	3.6	0.5-8.7	6.5	2.4-16.5	3.2	1.4-5.4	3.2	0.6-5.8
Monocytes	0.4	0.4	0.0-1.6	0.4	0.2-0.6	0.2	0.0-0.8	0.1	0.2-1.0
Normoblasts	15.0	33.1	22.4-53.2	27.2	24.2-44.0	33.0	23.8-53.2	28.9	10.0-59.6
Erythroblasts	1.7	4.9	1.8-13.0	3.1	0.2-8.6	6.2	2.8-14.0	3.0	1.2-5.0
Megaloblasts	0.2	1.5	0.0-3.4	2.6	0.0-4.8		1.0-3.2	1.3	0.2-3.2
Plasma Cells		0.5	0.0-2.0			0.5	0.0-1.8	0.3	0.2-1.8
Megakaryocytes				0.8	0.0-0.8	0.1	0.0-0.4	0.3	0.2-1.0

marrow to red marrow involving both the red and white cell precursors. The ideal method for the study of the bone marrow in this condition is by histological section after biopsy or bone marrow punch. Block, Jacobson and Bethard[124,125] have found that in about 80-85 per cent of the cases of polycythemia vera sections of the marrow from the sternum were diagnostic of the disease even though the patient had normal or subnormal hemoglobin values as a result of hemorrhage, phlebotomy or treatment with phenylhydrazine and could be differentiated from cases of secondary polycythemia. These authors described the marrow as being hyperplastic with a replacement of much of the adipose tissue by hematopoietic tissue. There was a hyperplasia of cells of the megakaryocytic, erythroid and myeloid series and a tendency for cells of the erythroblastic series to occur in small clusters. They found that following treatment with P^{32} the marrow was uniformly converted to a normal cellularity or slight hypocellularity, however a slightly increased percentage of normoblasts remained. Berlin in this laboratory studied 21 cases by the punch needle biopsy technique and found histological changes in agreement with those of Block and co-workers.[124,125] After P^{32} the effect was a reduction in the total volume of hematopoietic tissue with a reversion of the marrow to a normal or almost normal architecture. Thus sternal marrow puncture is of limited value but bone marrow sections are of great value in diagnosis and in assessing therapy.

Viscosity

The viscosity was determined in an Ostwald viscosimeter and compared to water at the same temperature. Figure 12 shows the viscosity of the blood as a function of the red cell count in millions. The coefficient of correlation between the viscosity and the red cell count is 0.95, which is significant. This may be of considerable importance in the pathogenesis of the thromboses and hemorrhages seen in this syndrome.

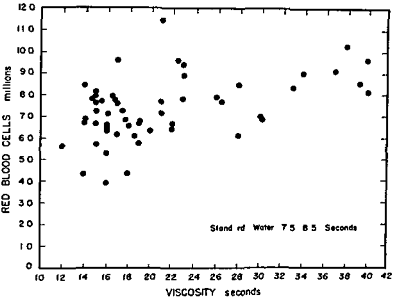


Fig 12 —The viscosity of the blood as a function of the red cell count in polycythemia vera with a water standard varying from 7 5 to 8 5 seconds

Iron Metabolism, Red Cell Production and Life Span

Until the studies of Huff Berlin and associates in this laboratory on red cell life[121] and red cell production [122, 123, 135] there had been speculation regarding the nature of the abnormality in red cell metabolism which leads to the polycythemic state Was red cell production increased or was red cell life increased? It is now clear that the gross and obvious abnormality of iron metabolism in polycythemia vera and also in secondary polycythemia is that associated with the increased production of red cells *Although there have been no reliable* determinations of total iron in the normal human body it is very probable that the amount does not exceed 4 to 5 grams and it is more likely near 2 5 to 3 grams A total red cell volume of two liters contains approximately 2 grams of iron The work of Finch Haskins and Finch [127] in which they were able to

produce an iron deficiency anemia with only a few repeated bleedings indicates the relative lack of iron available for hemoglobin synthesis as well as the relative inability of the body to absorb adequate amounts of iron From some of the Fe^{59} studies (in vivo scintillation counters placed over the liver and other sites) of normal subjects there is evidence that the turnover for nonpigmentary hepatic iron is only 4 per cent per day with the implication that 100-300 mg of such iron is present in the liver Nonhemoglobin pigmentary iron (cytochrome peroxidase and myoglobin) constitutes another small fraction of the total iron

The plasma iron amounts to 1 to 5 mg depending upon the plasma iron concentration and plasma volume It is the pool into which iron is dumped from the various cells and which furnishes an iron source for hemoglobin synthesis This pool of iron is complexed with globulin (globulin IV 7 Cohn) which limits the total quantity which may be present there at any time [1 8 134]

This limited knowledge of the quantities of iron present in hemoglobin plasma liver and the nonhemoglobin pigments furnishes a background for contrasting normal iron metabolism and that observed in polycythemia vera where the major iron compartment hemoglobin has been expanded as much as three or more times normal If the rate of disappearance of the globulin IV 7 Fe^{59} complex from plasma after intravenous injection in tracer doses the total plasma iron and the percentage of tracer Fe^{59} utilized in red cell formation are known the percentage of tracer Fe^{59} entering and leaving the plasma for red cell formation may be calculated This has been found in the normal to average 20 mg/day [135] However in an untreated polycythemia vera patient this value may be as high as 200 mg or more per day and is invariably elevated This excessive iron turnover is due in part to the increased total red cell volume However the rate of replacement of red cells is greater than would be anticipated on the basis of a red cell life span of 120

days This can be explained by the presence of a population of red cells with a shortened life span as shown below Similarly we have studied the life span of the red cell in Peruvian Indians living at 15,000 feet and although they have a marked secondary polycythemia there is no lengthening of the red cell life span Reynafarje studied a group of sea level dwellers taken to high altitude and found no lengthening of the life span of the red cell during acclimatization [135] There is no evidence for a lengthened red cell life span either in primary or secondary polycythemia [136, 138]

We have used the plasma iron turnover and red cell Fe^{59} uptake in the diagnosis and management of polycythemia vera in several ways Frequently patients are seen in whom it is difficult to decide whether the diagnosis should be primary secondary or relative polycythemia The total red cell volume may be increased 10–20 per cent and the symptoms minimal This arises from the fact that we have no very good index for comparison of blood volume from one individual to another unless one measures the total body fat and lean body mass The red cell production rate can be estimated from the turnover data obtained and the assurance to the physician and patient in knowing that there is likely to be no increase in the total red cell volume or that it will decrease is valuable information which can be gained by plasma and red cell iron turnover studies In untreated polycythemia vera the turnover rate is invariably high A second use made of iron turnover rates is in the assessment of the efficacy of therapy Again because of the slowness of net changes in the total red cell volume following treatment there may be a temptation for the physician to give additional therapy while in reality the production rate is normal or below normal and will eventually lead to the desired normal total red cell volume (Fig 13) In secondary polycythemia the plasma iron turnover is increased in direct proportion to the increase in total red cell volume whereas this is not true in the case of polycythemia vera (see above) The effects of changes in

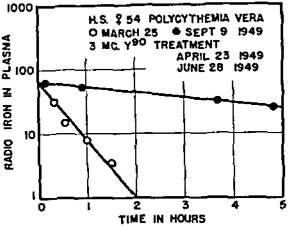


FIG 13.—The concentration of radioiron in plasma as a function of time before and after treatment The decrease in plasma iron turnover following treatment (black dots) is an index of the slowed rate of red cell production

barometric pressure and oxygen tension on hematopoiesis are reflected in the iron turnover rates much more quickly than in changes in the total red cell volume or in the morphology of the bone marrow [138] The latter is a very insensitive method of assessing bone marrow activity In the few cases studied inhaling 50 per cent oxygen was found to depress plasma iron turnover and red cell iron uptake in secondary polycythemia but not in polycythemia vera [139] which provides added evidence that the etiology of polycythemia vera is not on the basis of anoxia or hypoxia in the ordinary sense This does not rule out the possibility suggested by Reznikoff and associates [8] that the gas exchange in the bone marrow may be impaired thus leading to a local hypoxia

With the use of scintillation counters placed over the bone marrow liver and spleen for in vivo measurement of Fe^{59} the sites of red cell formation can be demonstrated [1, 13] A few patients with polycythemia vera have splenic and/or hepatic erythropoiesis while in most the excessive production is con

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pleen it is possible to differentiate between splenic erythropoiesis and excessive splenic red cell destruction (Fig. 14) These methods have also proved of great value in the study and differential diagnosis of various types of refractory anemias where it is important to determine whether the spleen is making red cells or destroying them and also in cases in which splenectomy is considered [12, 13, 140]

London et al [14] using N^{15} labeled glycine found that the life span of the red blood cell was normal in one patient with polycythemia vera In five patients studied by Berlin et al [15] following the administration of 100 microcuries of C^{14} labeled glycine there was a rapid rise in the specific activity of the hemoglobin followed by a fall and secondary rise (Fig. 15) This may be analyzed in terms of a population of cells consisting

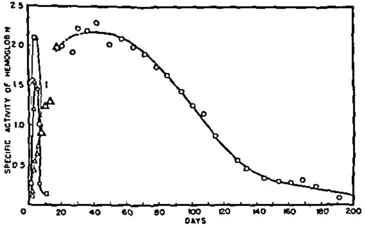


FIG 15 — The specific activity of the hemoglobin in a patient with polycythemia vera following the administration of 100 microcuries of glycine-2 C^{14}

○ = observed specific activity of hemoglobin

△ = calculated specific activity of long lived cells

□ = calculated specific activity of short lived cells

fined to the bone marrow The former have extremely large spleens and elevated white cell counts (20 000–40,000) with immature myeloid cells The distribution of "iron accepting bone marrow in those cases not having splenic erythropoiesis is usually normal although in some cases the long bones may be involved to an abnormally great extent In "splenic polycythemia as detected with Fe^{59} the bone marrow is usually found to be hypoplastic aplastic or fibrotic on microscopic section and it also fails to accumulate Fe^{59} as measured by the counter over the marrow indicating a paucity of erythropoietic tissue in the marrow (see CASE HISTORY LY) With this technique of in vivo counting by following the radioactivity present in the

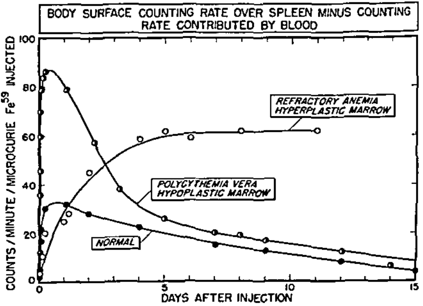


FIG 14 —By placing a scintillation counter over the spleen of a patient who has received a tracer dose of Fe^{59} it is often possible to differentiate between splenic erythropoiesis and splenic destruction of red cells The figure illustrates curves obtained in (1) a patient with polycythemia vera who has splenic production of red cells (2) a patient with anemia where there is destruction of red cells in the spleen and (3) the normal spleen curve

polycythemia vera is a neoplastic like disease rather than anoxic in origin If as Harrop and Heath suggest [4] there were decreased rates of diffusion of oxygen across the alveolar membrane some degree of oxygen unsaturation of the blood could occur even in the presence of increased availability of oxygen in the inspired air however several reports of arterial oxygen saturation in polycythemia vera show normal or near normal values [18, 141, 11] We have found the mean arterial O_2 saturation in 59 patients to be 92 2 per cent as compared to 95 1 per cent in 18 normals Also the possibility would exist as Reznikoff and his associates believe [48] that gas exchange in the bone marrow may be impaired leading to a local anoxia and obviously increasing the blood oxygen content might not necessarily increase the supply of oxygen delivered to the bone marrow tissues and a local marrow hypoxia could occur However Schwartz and Stats[143] found oxygen saturation of sternal marrow blood to be slightly higher in polycythemia vera than in controls while Berk and co workers[144] found no differences There is thus no demonstrable bone marrow hypoxia in polycythemia vera such as occurs in secondary polycythemia [144] It seems unlikely that anoxia is at the root of the condition Also the concomitant increase in the number of white cells and platelets the frequent concurrence of leukemia the failure of 50 per cent oxygen administration to depress the rate of red cell production as measured with Fe^{59} [139] and the evidence for abnormal red cells[121] all point to the neoplastic like nature of polycythemia vera

As mentioned above Harrop and Heath [4] suggested that inefficient diffusion of gases across the alveolar membrane might be at fault Studies from this laboratory by Jones Berg et al on normal subjects on patients with pulmonary disease and on patients with polycythemia vera are of interest in this connection [5, 145, 146, 147] These investigations have shown a decreased gas exchange rate (nitrogen argon krypton xenon and CO_2) in patients with pulmonary fibrosis but yielded no clear cut

of both long lived and short lived red cells It is the rapid turn over of the short lived red cells which accounts for the large amount of iron utilized by these patients Thus the data on iron metabolism and red cell life are compatible if one thinks of the cells as being divided into two population classes one with a short life span and the other normal [11] Our studies indicate the presence of an abnormal type of red cell from the standpoint of life span These cells probably function normally, however, in the transport of oxygen and carbon dioxide

In summary abnormalities in iron metabolism in polycythemia vera are related to (1) excessive production rates, (2) shortened life span of erythrocytes and (3) abnormal sites of red cell formation

Anoxia as a Possible Cause of Polycythemia Vera

Since it has been known for many years that the partial pressure of oxygen of the inspired air has a direct effect on the rate of red cell production [2] one attractive theory for the cause of polycythemia vera is that there is bone marrow hypoxia Two pieces of work are of interest in this regard one that of Harrop and Heath [4] who found a decrease in the rates of diffusion of respiratory gases across the alveolar membrane They suggested that this might lead to a slight degree of oxygen unsaturation of the blood which in turn directly or indirectly would lead to stimulation of red cell production The other is the work of Reznikoff and co workers[48] who thought that capillary fibrosis and arteriolar sclerosis in the bone marrow vessels might lead to bone marrow hypoxia and thus cause increased erythropoietic activity

As mentioned in the section on iron metabolism inhaling 50 per cent oxygen depressed the plasma iron turnover and red cell uptake of iron in secondary polycythemia but did not slow these rates in polycythemia vera,[139] supporting the view that

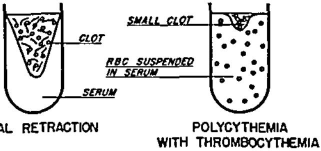


FIG 16—A schematic representation of normal clot retraction and clot retraction in polycythemia vera with thrombocythemia

hibiting therapy directed toward the reduction of both platelets and total red cell volume With the increased blood volume and capillary distention it is not surprising that hemorrhage is common in these patients With reference to the use of anti coagulants in the possible prevention of thrombosis in various arteries in patients with polycythemia vera the author has tried such anticoagulants in only one case and there were no untoward effects However Wasserman has reported that it is unwise to use anticoagulants in patients with polycythemia vera because of the danger of bringing on hemorrhages [153] How ever proper control of the platelet count and red cell mass is a successful way of preventing thrombosis so that anticoagulants are not necessary and are probably dangerous

Of interest in this connection is the observation by Miranda[74] that in inhabitants of the Alta Plano in Peru who have large blood volumes there is also an increased incidence of hemor rhagic phenomena such as gastric hemorrhage and hemorrhage from ruptured varicose veins in the lower extremities

Therapy and Its Effects

It seems clear that the primary abnormality leading to the syndrome of polycythemia vera is an increased activity of the

evidence that patients with polycythemia vera have any decrease which could not be explained on the basis of their age

Coagulability of the Blood

A paradoxical situation is present in patients with polycythemia vera in that there is both a high incidence of hemorrhage from various vessels in the body, such as cerebral and gastric vessels and also a high incidence of thromboses[44 45 46 81 110 149] As pointed out above blood viscosity is increased and there is often an elevation of the platelet count Routine studies of blood coagulability reveal no apparent abnormalities in clotting or bleeding times Bjorkman[149] and Fiehrer[150] have described in coagulability of the blood of patients with polycythemia vera due to fibrinogenopenia In both instances only small numbers *of cases were studied and thus the incidence of this complication* in a large series of cases of polycythemia vera is unknown We have not observed incoagulability of the blood in this condition In 34 cases the clotting time was determined in Lee White tubes and found to average 7 57″ the bleeding time was found to average 3 8 in 10 cases Rosenthal in our laboratory studied blood coagulation in patients with polycythemia vera and obtained some very interesting data relating to the problem of thrombosis and hemorrhage in this condition[151 15] In a group of 39 patients 33 per cent had histories of either thromboses or hemorrhage and 36 per cent of the group had an elevation of the platelet count above 400 000 when first seen by us Thirty one per cent (12 cases) had an increase in clot retraction rate and in 9 of these 12 the platelet counts were above 400 000 However the clot is often fragile imperfectly formed di olves easily and has poor retraction (Fig 16) The rapid but defective clot retraction associated with the high hematocrit elevated platelet count and increased blood viscosity is probably eti ologically related to the frequent complication of both throm bosis and hemorrhage It will be pointed out later that the e complications can be markedly reduced by proper marrow in

there is always the danger of getting the colloid outside the vein after intravenous injection, with a resulting local radiation necrosis, we abandoned the use of these other isotopes in favor of P^{32} in 1947.

A few patients have been handled by venesections alone, and these have usually been relatively young patients or the rare patient easily controlled by infrequent venesections.

In general, after completion of the history, physical examination and laboratory studies, the patient is given 3 to 5 millicuries of P^{32} as the first dose. If the total red cell volume is extremely high or if there has been a history of thromboses or hemorrhage, it sometimes seems advisable to perform several venesections on successive days prior to therapy with P^{32}. After P^{32} therapy the patient is observed at weekly to biweekly intervals, particularly with reference to changes in symptoms and white cell and platelet counts. After 10 to 12 weeks the patient is again completely re-evaluated from the standpoint of hematological and symptomatic improvement. When necessary, a second dose of 3.5 millicuries of P^{32} may then be administered. The patient is again followed carefully, and in a relatively small number of cases further treatment with P^{32} may be needed to produce the first remission. In the older patients we tend to use somewhat smaller dosages and at less frequent intervals, since they are often more radiosensitive. In others, single doses of 4.5 and in rare instances 6 mc. are needed.

An analysis of 300 courses given to a group of 139 patients shows that an average of 6.7 millicuries of P^{32} per course was given. A course of therapy has arbitrarily been set as the total amount given over a six month period. For the results of the effects of therapy on the physical findings and the blood, in each instance the maximum change after the initiation of therapy was used. The time of such effect after therapy or the time of reversal of a given finding before the next course of therapy has

bone marrow not limited to the red cell series only but including the white cell and platelet precursors This increased cellular activity may be related to a neoplastic like metabolism of these bone marrow precursors and classified as uncontrolled growth Or the bone marrow simply may be responding to stimuli, either nervous or humoral coming from other areas of the body The logical way of treating this condition then would be to reduce the bone marrow metabolism to normal or to inhibit the nervous or humoral stimuli reaching the bone marrow The author has discussed such humoral, bone marrow stimulating agents above No successful therapy on this basis has eventuated up to now, however and relatively crude methods of therapy such as venesections, phenylhydrazine and other chemical agents and spray, total body Roentgen irradiation have been the conventional methods of treatment

Since the introduction of radiophosphorus for the treatment of polycythemia vera in 1938,[83]* practically all patients with polycythemia vera studied by us have been treated by P^{32}, in general intravenously either alone or in combination with venesection In over 60 per cent of the total P^{32} was the first form of therapy given We regard radioactive phosphorus as superior to other available isotopes As long as 15 years ago we tried (both in chronic leukemia and polycythemia vera) strontium 89 yttrium 90 and chromic radiophosphate in colloidal form, and other colloids[154, 155] since they localize primarily in the bone marrow spleen and liver and they seem to be equally effective as P^{32} in bringing about a remission However since the end results are no better than those obtained with P^{32} since more labor is required for their preparation and since

* Although we made the first therapeutic application of artificial radioactive isotopes on Christmas Eve of 1936 in the treatment of a patient with chronic leukemia the first use of an artificially produced isotope which resulted in the control of a disease so that a nearly normal life expectancy was achieved was the use of radioactive phosphorus in the treatment of polycythemia vera Our first polycythemia vera patient treated in 1938 is still living at the age of 77

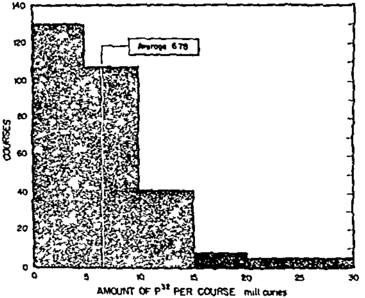


FIG 18—The amount of P^{32} per course in polycythemia vera patients

ally ranges between six and ten months Once the patient is brought into remission the interval is usually about 3½ months and it is possible for some patients to continue without further treatment for much longer periods (see Case History S H Fig 32) When the patients were initially seen they were usually given a dose of 3 millicuries of P^{32} and observed for a period of three to four months and perhaps given a second dose then * Once active therapy has begun we do not push it to the limit but slowly bring the patient into remission This may require from 12 to 18 months or in a few instances as long as two years before the red count is finally brought down to or below 5 5 million This does not imply that no effect is seen immediately since the criterion for remission is noted as being 5 5 million Many patients with markedly elevated counts will be brought down to 6–7 million and then later gradually brought

* We are tending to give 3½–4½ mc now for the first dose

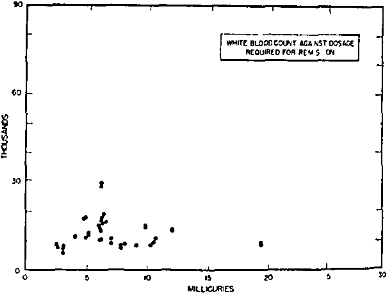


Fig 17 —The amount of P^{32} required for a remission as a function of the initial white count

not been determined Figure 17 shows that there is no good correlation between the amount of P^{32} required and the white cell count before treatment Figure 18 presents the amount of P^{32} in individual courses The largest number of courses were in the range of 5 millicuries or less but there was also a large number in the 5–10 millicurie range A smaller number of courses consisted of 10 15 millicuries with a very few in the 15 30 range The average total dose for all courses was 6 7 millicuries

Figure 19 presents an analysis of the treatment used Venesections were usually carried out one or two days before or after P^{32} administration in those patients with severe symptoms or those with thrombotic histories when it seemed desirable to bring down the total red cell volume to near normal levels within a short period of time To do this three or four venesections at frequent intervals were often necessary When active therapy is begun in patients in relapse the interval between courses usu

clear that most of the severe symptoms are due to the marked increase in the volume of blood especially of the circulating red cells Certainly in the average patient when the total volume of red cells is returned to normal the symptoms of the disease vanish with the exception of a few such as redness of the hands and feet in some cases and other symptoms of a mild nature which one would expect to be present in people in this relatively older age group

It is of course obvious that in any group of people with an average age greater than 52 many of them will suffer from the various degenerative conditions of aging such as atherosclerosis hypertension and cancer The latter will be discussed later under causes of death and life expectancy However with reference to hypertension there seem to be two types—one affected by a decrease in the blood volume and the other not and from the physiological standpoint these findings are of great interest The relationship of hypertension to blood volume has been studied by my associate Prentice et al [16] and will be discussed in more detail below In the type of hypertension unaffected by reduction of the blood volume symptoms associated with hypertension such as dizziness ringing in the ear and headache would be expected to persist after the polycythemia had been brought into control and this probably accounts for many of the continuing symptoms

The effects of therapy on the principal symptoms are as follows (symptoms have been classified as improved unchanged or worse) With reference to headache it was noted that 92 per cent showed symptomatic improvement and 8 per cent were unchanged With respect to dyspnea 81 5 per cent improved 13 per cent unchanged and 5 5 per cent worse vertigo 80 per cent improved 15 5 per cent unchanged and 4 5 per cent worse eye complaints 85 per cent improved 5 per cent unchanged and 10 per cent worse stomach complaints 74 per cent improved 13 per cent unchanged and 13 per cent worse and precordial chest pains 76 per cent improved 16 per cent unchanged and 8 per cent worse In general the symptoms

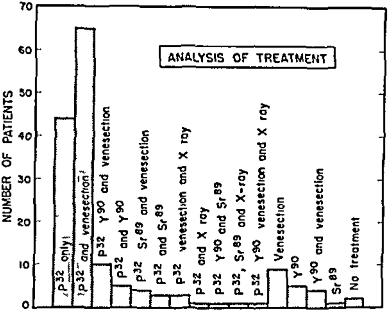


Fig 19 —An analysis of the types of therapy used for the treatment of polycythemia vera

down to levels of complete remission Thus the relatively short interval (6–10 months) between courses of therapy in patients in relapse is merely a reflection of caution in treating the e patients and does not imply a necessity for frequent therapy In a disease which usually has been long in developing the author does not hesitate in most patients to bring it under control slowly providing the danger of thromboses is minimized by bleeding and control of the platelet count If larger doses of P^{32} had been given the average interval between courses of therapy would have been much greater At present (1955) we are tending toward larger individual doses However the dangers of an excessive original dose are exemplified in Case A I (See *Hemotological Changes after Therapy*)

Although the etiology of this disease is not known and if it is granted that some of the symptoms may antedate the increase in red cell count and total red cell volume it has seemed to us

clear that most of the severe symptoms are due to the marked increase in the volume of blood especially of the circulating red cells Certainly in the average patient when the total volume of red cells is returned to normal the symptoms of the disease vanish with the exception of a few such as redness of the hands and feet in some cases and other symptoms of a mild nature which one would expect to be present in people in this relatively older age group

It is of course obvious that in any group of people with an average age greater than 52 many of them will suffer from the various degenerative conditions of aging such as atherosclerosis hypertension and cancer The latter will be discussed later under causes of death and life expectancy However with reference to hypertension there seem to be two types—one affected by a decrease in the blood volume and the other not and from the physiological standpoint these findings are of great interest The relationship of hypertension to blood volume has been studied by my associate Prentice et al [120] and will be discussed in more detail below In the type of hypertension unaffected by reduction of the blood volume symptoms associated with hypertension such as dizziness ringing in the ears and headache would be expected to persist after the polycythemia had been brought into control and this probably accounts for many of the continuing symptoms

The effects of therapy on the principal symptoms are as follows (symptoms have been classified as improved unchanged or worse) With reference to headache it was noted that 92 per cent showed symptomatic improvement and 8 per cent were unchanged With respect to dyspnea 81 5 per cent improved 13 per cent unchanged and 5 5 per cent worse vertigo 80 per cent improved 15 5 per cent unchanged and 4 5 per cent worse eye complaints 85 per cent improved 5 per cent unchanged and 10 per cent worse stomach complaints 74 per cent improved 13 per cent unchanged and 13 per cent worse and precordial chest pains 76 per cent improved 16 per cent unchanged and 8 per cent worse In general the symptoms

improve proportionally to the degree of return of the red cell count and total red cell volume to normal level

Gastric and other hemorrhage has been discussed above under symptoms and signs At some time following the initial examination and during observation and treatment by us, six additional patients had gastric hemorrhage In three this occurred while the patient was in hematological relapse, and in two of these the history was compatible with that of a peptic ulcer In one of these latter two a duodenal ulcer was demonstrated by x ray examination of the gastrointestinal tract Two patients were in hematological remission at the time of gastric bleeding One of these had a history of a previous operation for perforation of a duodenal ulcer The other had two episodes of gastrointestinal bleeding at one time with symptoms of postprandial epigastric distress compatible with those of a peptic ulcer but x ray examination showed no evidence of an ulcer in this patient The sixth patient died following a massive gastrointestinal hemorrhage and at autopsy chronic duodenal ulcers were found The hematological status at the time of bleeding is unknown

Three of the patients have had during observation by us classic attacks of gout treated successfully by colchicine and P

*Changes in Physical Findings After Therapy**

The changes in physical findings have been analyzed in the first group of 148 patients treated with radioactive isotopes

The ruddy cyanosis which was apparent in 88 of the 148

* Although most of these patients returned for follow up care at frequent intervals there are some in which it has been necessary to secure information on the effects of therapy from the patient's physician This in large measure accounts for our inability to give complete details on the results of therapy in some patients It is our belief that those patients adequately followed and controlled (not by long distance by another less interested physician) do better symptomatically and from the standpoint of life expectancy This condition is one requiring constant supervision if long life of the patient is to be achieved

patients treated was improved as a result of therapy in 36 and remained the same in 11. In 42 cases the record was unsatisfactory. Thirty two of the 36 had a fall in the red count (average, 1.56 million) and four had an increase (average 340,000).

The lungs and the skeleton from the radiological point of view are of interest in that changes are occasionally found. In the case of the lungs it is not unusual for the roentgenologist to point out increased vascular markings as seen in the chest film. These may disappear with the return of the red cell volume to normal. Hodgson et al.[156] have studied the skeletal roentgenologic findings in a large group of patients and found no characteristic changes present. In our experience with 250 or more patients skeletal x-ray examination has been made in some cases (usually not complete skeletal surveys) and we have found in three instances eburnation of cortical bone with increased cortical laying down of bone. This makes one suspect the relationship of polycythemia vera to these changes.

In this group there were 95 patients with palpable spleens prior to therapy. As a result of therapy the spleens decreased in size in 84. This decrease in size was such that in 62 of the 84 it was no longer palpable. In 6 patients the spleens did not decrease in size; in 4 there is no further record of spleen size and in one it increased. In this latter case the increase was not great.

In 31 patients the spleen was not palpable at the time of the initial physical examination and did not become palpable during the course of the disease observed by us. In 22 patients the spleen became palpable following the initial examination and in 11 of these the spleen changed from being nonpalpable to being just barely palpable on deep inspiration. Thus it is quite probable that in many of these 11 patients the spleen might have been palpable at the time of the initial physical examination and that it was a question of the examiner being unable to palpate it or thinking it was questionable. As compared to that at the time of the initial examination 10 of these 11 patients

had significantly lower red cell counts at the time the spleen became palpable and in 1 it was unchanged

In the other 11 patients—those in whom the spleen became definitely palpable after the initial physical examination the red cell count was increased in 2 patients and decreased in 9 It should be noted that in 4 of these cases the association of palpability of the spleen occurred with the development of the *chronic myelogenous leukemic phase of polycythemia vera* There are 7 in whom the spleen became definitely larger during the course of observations but who did not develop leukemia

With reference to the 84 patients having palpable spleens at the initial examination in which a decrease in spleen size was noted following P^{32} therapy 68 had lower red cell counts with therapy (average of 1 7 million and ranging up to 5 83 million) and 16 patients had an increase in the red cell count (average of 750 000 and ranging from 60 000 to 3 09 million) In only four cases was the increase greater than 1 million These counts were done at the time the spleen size was minimal

The liver was palpable in 52 of 159 patients at the initial examination All but 4 of the 52 received P^{32} and the liver size decreased in 21 of the treated patients There were 28 patients in whom the liver was not palpable at the initial examination, but later became palpable Excluding one of the 28 patients who was treated by venesection only 5 patients had an increase in the red cell count and 22 had a decrease The increase in red cell count was never more than 700 000 and averaged 450 000

Seventy one of the 144 treated patients for whom blood pressure records are available were hypertensive at the time of the initial examination Following therapy 35 showed a significant reduction in the blood pressure (a decrease of 20 mm systolic or more) with the following changes in the red cell count in 24 patients a reduction was noted in 7 the change was not significant and in 4 the count was slightly elevated

In 22 of the 73 patients who were normotensive at the time

of the initial physical examination there was an increase in the blood pressure later to over 150/90 In eight of these patients the red cell count was either approximately at the same level or very slightly elevated the maximum elevation being 800 000 In the other 14 patients there was some reduction in the red cell count although the blood pressure had risen Thus both an increase and a decrease in the blood pressure can be seen with a decrease in the red cell count and blood volume It seems clear to us however that in some patients the decrease in blood pressure is the result of decrease in blood volume but in others there seemed to be no relation between the blood volume and the hypertension The relatively high incidence of hypertension can be attributed to at least two factors First in this age group one would expect to find a considerable number of individuals with mild to severe essential hypertension Second the probable slowed blood flow in the cortical arterioles of the kidney might lead to anoxia of the kidney cortex with the liberation of a hypertensive humoral agent The case history A F exemplifies the problem of patients having polycythemia vera and severe hypertension unrelated to blood volume increase In a special study by my colleague Prentice[120] there was again no uniform relationship between blood volume hypertension and splenomegaly

Hematological Changes After Therapy

In 94 per cent of the 148 patients treated with radioactive isotopes there was a remission using a red cell count of 5 5 million as representing a remission (for a typical example see Figure 20) A further breakdown of this unselected group of patients showed that of 148 patients 118 had red cell counts that fell to 5 5 million or less after the first course of therapy of which only three fell below 3 5 million Twenty eight patients had a red cell count above 5 5 million after the first course of therapy In two patients the record was unsatisfactory However it should be further noted that of these 28 patients 50

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With reference to the 84 patients having palpable spleens at the initial examination in which a decrease in spleen size was noted following P^{32} therapy, 68 had lower red cell counts with therapy (average of 1.7 million and ranging up to 5.83 million) and 16 patients had an increase in the red cell count (average of 750,000 and ranging from 60,000 to 3.09 million). In only four cases was the increase greater than 1 million. These counts were done at the time the spleen size was minimal.

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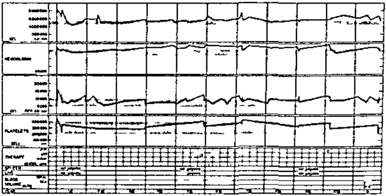


FIG 20 —The clinical course of Patient J C illustrating a good remission following therapy with I^{131} or Y^{90}

per cent had counts between 5 5 and 6 0 million and there were two patients who died one of carcinoma of the pancreas and one of congestive heart failure, within two months following completion of therapy so that over 90 per cent of the patients responded satisfactorily after the first course of therapy It again should be emphasized that our conservatively small doses do not cause all of the patients to return to normal red cell values after the first course of therapy

The initial white cell counts in these 159 patients ranged as high as 65 000 and averaged 16 900 Of the 148 patients treated with radioactive isotopes 119 had white cell counts greater than 10,000 before therapy with P^{32} After the first course of therapy 59 of these had white cell counts in the 5,000–10 000 range 30 had counts which temporarily went below 5 000 of which 16 went below 3 500 and 16 continued to have counts over 10 000 In the latter 16 reductions in the white cell count did occur, but not to below 10 000 In 14 of the cases the data are not complete enough for accurate analysis The striking finding, of course is the frequent conversion from an elevated to a normal count as the result of therapy with P^{32} and we have pointed this out previously [3] Good comparative records of white

counts were available in 82 patients in relapse after the first course of therapy and these showed that in only 10 did the white cell counts rise significantly (4 000 or more) above the values observed prior to the first course of therapy In the majority of the treated cases the white cell counts did not subsequently rise to the levels observed at the initial examination

White cell differential counts were considered abnormal if a metamyelocyte or a less mature cell of the myeloid series was present in the peripheral blood Seventy eight patients of 108 treated went from abnormal to normal differentials five had metamyelocytes and showed no significant change and six had myelocytes and showed no significant change There was one patient with progranulocytes who showed no change and one patient with myeloblasts who showed no change In four patients myeloblasts disappeared and only myelocytes remained two patients went from myelocytes to metamyelocytes as the most immature cell and two from progranulocytes to myelocytes as the most immature cell Thus 86 patients showed significant improvement in the differential in the sense that there was a shift to the right and 21 patients showed no significant improvement Of these 21, the cell type remained essentially the same in 13 while in 8 there was a shift to the left In one patient follow up was inadequate

With respect to platelet counts a level of 200 000 to 300 000 has been arbitrarily set as normal Of the 148 patients treated there were 27 with an initial count in the normal range 56 per cent of whom had had previous therapy with P^{32} x ray phenylhydrazine or phlebotomy 14 below normal 80 per cent having had previous therapy 68 above normal 86 per cent having had previous therapy and 39 on whom platelet counts were not done on the date P^{32} was administered Following therapy there are satisfactory records on 97 patients 35 (36 per cent) were within normal range 57 (59 per cent) were below normal 46 between 100 000 and 200 000 and 11 between 60 000 and 100 000 and 5 (5 per cent) were above normal

Thus, it is strikingly seen that both the white cell count and the platelet count are usually brought down to a normal range following therapy with P^{32} In no patient was there observed all of the following a decrease in the red cell count below 3 500 000 a white cell count below 3 500 and a platelet count below 100 000 Thus we have seen no instance of severe pancytopenia as a result of P^{32} therapy, and we have not observed one fatality due to permanent depression of any one of the three elements We have however had three instances of purpura due to platelet depression (one following a dose as low as 5 millicuries) with recovery but no untoward complications from red cell or white cell depression If a higher dosage schedule had been used more such cases would have been observed Case history A L which follows is an example However it is also true that some of the longest remissions have followed excessive bone marrow depression

Patient A L

This 48 year old woman was first seen by the author in Italy in September 1954 Three months previously she had received her first dose of P^{32} in a European clinic and this single dose of 5 mc proved excessive in her case A marked depression of the red white and platelet counts had resulted reaching a low of RBC 2 9 million WBC 2 400 and platelets 100 000 in late September Ecchymotic spots appearing on the lower legs and arms could be attributed to platelet depression The only other positive findings by the author were a generalized pallor and slightly enlarged spleen With the administration of vitamin B_{12} and liver extract but not due to this therapy the patient made a good recovery

Her illness had been diagnosed ten years previously when she consulted a physician following an episode of visual disturbances and vertigo Other symptoms reported were nausea headache pruritis and a feeling of apprehension At that time injection of the eyes and ruddy cyanosis were observed as well as splenomegaly which the patient reported had existed from the age of 18 A red cell count of 7 54 million and hemoglobin of 130 per cent were found and the bleeding and coagulation times were prolonged A study of the capillaries showed them to be irregular tortuous and thickly dilated In some of the arches the stream of red cells was almost stagnant She received three courses of x radiation to the long bones in late 1945 early 1946

and early 1947 respectively On each occasion the red count fell to the 5 million range but would rise again to the 6–7 million level within a few months In 1951 and again in 1953 reductions in the red count were achieved by injections of chloramin but the patient reported reactions of nausea and chilling following its use *It is interesting that during two pregnancies the* red count remained in good control without therapy suggesting the possible value of conjunctive hormone therapy in her case

The dramatic depression of the bone marrow in response to a large dose of P^{32} in this case illustrates the necessity for proceeding with caution in radiophosphorus therapy While many of our patients have received a total dose of 8 mc in one course of therapy in divided doses without ill effect we find it safe to begin with an initial dose of 3 [illegible] mc to avoid bone marrow depression in the radiosensitive patient This patient is now well without further therapy Usually when there has been excessive marrow depression the remission lasts longer

In a special study by my colleague Prentice[120] 44 interval determinations of the blood volume were made in 20 patients with polycythemia vera during therapy over a period varying from 3 to 20 months There were 12 males and 8 females in this group Two dominant patterns of change in blood volume were found the frequency of which was approximately equal (1) a parallel fall of total red cell volume and plasma volume and (2) a fall in total red cell volume with a reciprocal rise in plasma volume When the plasma volume rises reciprocally the magnitude of change is considerably greater than in those cases in which it falls The pattern of change does not remain constant in individuals patterns 1 and 2 often appearing in the same patient at different times As a result of therapy the changes in the blood volume showed consistently a decrease in the total red cell volume with the change in plasma volume either increasing reciprocally or decreasing The resulting change in blood volume generally is a decrease In these 20 patients, the size of the spleen rapidly decreased to a marked degree in all but one of the patients in whom the organ was originally palpable and remained small for varying periods The changes in spleen size did not appear to be a direct function of blood volume

Thus it is strikingly seen that both the white cell count and the platelet count are usually brought down to a normal range following therapy with P^{32} *In no patient was there observed all* of the following a decrease in the red cell count below 3,000 000 a white cell count below 3 500 and a platelet count below 100,000 Thus, we have seen no instance of severe pancytopenia as a result of P^{32} therapy and we have not observed one fatality due to permanent depression of any one of the three elements We have however had three instances of purpura due to platelet depression (one following a dose as low as 5 millicuries) with recovery but no untoward complications from red cell or white cell depression If a higher dosage schedule had been used more such cases would have been observed Case history A L which follows is an example However, it is also true that some of the longest remissions have followed excessive bone marrow depression

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when he had severe pleuritic pain in the right lateral costal region and a diagnosis of a small pulmonary infarction was made. The patient was heparinized and dicumarolized and dismissed two weeks later.

At the time of surgery the patient had received no treatment for her polycythemia vera, the diagnosis having been made only one month earlier, and she was not seen by us until May 1952. Her complaints then were head and neck pain and lassitude. The spleen was enlarged. The total red cell volume was 37.9 cc./kg. of body weight (normal range 24–33), and her red cell counts were also only moderately elevated. They ranged between 5.5 and 6.5 million for the next few months with hemoglobin ranging between 10 and 13 grams and white counts between 11,600 and 17,200. Her platelet counts were consistently elevated during this period, ranging from 510,000 to 800,000. Following her first P^{32} therapy (3 mc.) in October 1952 the platelet counts and white counts dropped to normal levels and have remained there to the present time. A second dose of 3 mc. of P^{32} was given in March 1953, with some reduction of the red count and hemoglobin. In July 1953 the patient became slightly anemic as the result of rectal bleeding and a hemorrhoidectomy. Following surgery her course was uneventful and she has required no further therapy up to May 1954, although there has been a gradual increase in her total red cell volume and she may require therapy soon.

F. W., a 52-year old white man, underwent an elective herniorrhaphy in February 1952 and a transurethral prostatectomy was performed a few days later. The patient received 1 unit of whole blood and his postoperative course was very good except for a urticarial reaction attributed to penicillin and some frequency of urination attributed to a hypertrophic bladder wall.

The patient's polycythemia was in good control at the time of surgery. He had first been seen by us a year before, at which time the positive physical findings were ruddy cyanosis, injection of the sclera and mucous membranes of the mouth and pharynx, widespread skin lesions which cleared with P^{32} therapy, mildly sclerotic peripheral vessels, slightly enlarged spleen and right inguinal hernia. His blood count showed: RBC 6.31 million, hemoglobin 21.6 grams, platelets 140,000 and WBC 13,500. The total red cell volume was excessive, 68.5 cc./kg. of body weight (normal range 24–33). Blood oxygen saturation was normal. The patient was given 3 mc. of P^{32} in February 1951. He showed an excellent response to therapy and his next blood volume six months later showed a total red cell volume of 31.6 cc./kg. He continued in remission through the period of surgery and required no further therapy until May 1952.

W. C., a 71-year-old man with polycythemia vera complicated by generalized arteriosclerosis, senile emphysema, and a history of myocardial in

Studies of groups of patients at various time intervals following the completion of therapy shows that there is no significant change in the bone marrow puncture differential as a result of therapy [20] We have found the bone marrow puncture differential to be of little value in the diagnosis of polycythemia vera or in its management except in cases of leukemic transformation of the bone marrow Bone marrow biopsy, however, gives valuable diagnostic information and we have confirmed the findings of Block et al [124, 125] that there is conversion of the bone marrow to normal or slight hypocellularity with P^{32} therapy

Surgery in Polycythemia Vera

Major or minor surgical procedures may be necessary in patients suffering from polycythemia vera First, in uncontrolled or untreated patients emergency surgery for many reasons may have to be considered It is not unusual in the history of a patient with this disorder to find that it was diagnosed only after intractable bleeding from a tooth extraction If emergency minor or major surgery must be performed, it is important first to bring down the total red cell mass by a series of venesections, since these patients are notable for their bleeding tendency at the time of operation Second in patients with adequately controlled polycythemia emergency or elective surgery minor or major may be indicated In our experience if the total red cell volume and platelet counts are normal there is no more morbidity or mortality from such surgical procedures than in any other similar age group

The following case histories are illustrative

M S *a 41 year old woman was hospitalized for severe uterine bleeding* in March 1952 and an emergency supravaginal hysterectomy was done two days later The pathologic diagnosis was submucous uterine fibromyomata Before surgery her red cell count was 6 69 million hemoglobin 16 grams and white count 18 250 Following surgery and four transfusions of whole blood her red cell count was 2 75 million hemoglobin 7 6 grams and white count 14 650 Her postoperative course was uneventful until the sixth day

polycythemia treated with anticoagulants with subsequent hemorrhage which was controlled by K₁ oxide or protamine however I am loathe to use anticoagulants in any polycythemia vera patient with a hematocrit over 50 In untreated cases with high counts and thromboses I prefer small phlebotomies followed by a myelosuppressive agent

With reference to surgery Wasserman has recently reviewed 142 of his polycythemia vera patients 21 of whom had surgery He states that Forty eight per cent of these developed severe complications and about half of these died following surgery This is a fantastic morbidity and mortality and is partially related to the level of the blood values Thirty eight per cent had severe hemorrhage two patients had pulmonary embolism and one died of shock It would appear that any disturbance in the vascular system in polycythemia vera will cause serious complications Although I felt that surgery and polycythemia were incompatible obtaining this factual data has solidified my stand in this matter I refuse to permit any elective surgery in my cases treatment for control of the polycythemia must precede elective surgery and emergency surgery is always preceded by venesections if possible *

The Problem of Leukemia in Polycythemia Vera

The chief if not only stumbling block in achieving a normal life span in these patients is the development of leukemia or allied complications It has been frequently discussed in the literature [3] Graham[36] found an incidence of 24 per cent Tinney Hall and Giffin [34] 17 per cent Wasserman[153] an incidence of 11 per cent of acute myeloblastic leukemia in a series of 64 cases in a series of 15 cases Minot and Buckman reported an incidence of 20 per cent Tischendorf and Herzog[37] in a series of 14 patients 21 per cent These figures are minimal since in none of these reports were all the patients in the group observed throughout the entire course of the disease It thus ap

L I Wasserman Complications of surgery in polycythemia vera (To be published)

farction was hospitalized for a segmental resection of a carcinoma of the bladder and a supra pubic prostatectomy in June 1953. His polycythemia was not in ideal control at the time and severe bleeding was encountered. The hemoglobin fell from the pre-operative level of 17.4 grams to 9.2 grams on the third postoperative day (500 cc. of whole blood had been given). On dismissal and after having had 2,500 cc. of whole blood transfusions the hemoglobin had again risen to 13.7 grams. During the next nine months the patient received a total of 5 mc. of P^{32}. In April 1954 he was again hospitalized for fulguration of three small papillary carcinomatous areas of the bladder but there was no blood loss at this time.

In the author's experience, except for mechanical reasons there is no indication for splenectomy in polycythemia vera unless the spleen can be related to a hemolytic syndrome.

Anticoagulants

Although a few cases in our series were given anticoagulants in connection with surgical procedures our policy has been to urge extreme caution in their use. My former colleague Wasserman[133] has recommended the use of heparin over other agents because it is easier to control. He states: "Within a few hours the effect is well spent and if protamine is used as an anti heparin agent the coagulation time is reduced to normal almost immediately. With prothrombin reducing agents the problem is more complex. About one third of our patients with polycythemia of more than a few years duration and inadequately treated have a slightly increased prothrombin time (14–18 seconds as contrasted with a normal of 11–12 seconds). Although this may not appear to be of any great import, nevertheless it is probably significant of defective liver function due either to the myeloid metaplasia, sluggish blood flow or anoxemia. These patients are frequently extremely sensitive to dicumarol and dicumarol like drugs. Although the dicumarol effect in normal patients can easily be counteracted by K_1 oxide, in polycythemia the slight prolongation of the prothrombin time persists and this factor together with the distended capillaries and the increased red cell mass may give rise to continued hemorrhage. I have observed a few cases of

leukemia.[illegible] In the present group treated with P^{32}, 73 have died, 16 with leukemia. This may well represent a lower incidence of leukemia than reported in other groups since these patients have been followed throughout the entire course of their disease, while in the other series the figures quoted do not represent the maximum incidence. Tinney et al.[illegible] have shown that there is a very high incidence of leukemia in those individuals surviving more than 10 years, and if these other larger series were to be followed until the death of all the patients, the incidence of leukemia would undoubtedly be much higher than reported. He demonstrated that in their group of long duration, treated with x irradiation, phenylhydrazine or phlebotomy, that is, in those patients who have lived 10 years or more, five out of eight cases (62 per cent) died of leukemia, while in those patients who survived more than 15 years, 80 per cent (4 out of 5) died with myelogenous leukemia. On the other hand, the comparable data from our series show that of the 65 living patients who had had polycythemia 10 years or more, only 9 (14 per cent) now have a leukemoid picture, and of the 28 who have died after having had the disease for ten years or more, 10 (36 per cent) have died of leukemia. Of those who have had the disease 15 years or more—and it should be pointed out that these are the more truly long duration cases since the median survival in this series is over 13 years—only 3 of 29 living patients (10 per cent) now have a leukemoid picture, and of the 11 deaths, only 4 (36 per cent) were attributed to leukemia.

Our relatively lower incidence is probably the result of the lowering of the white cell count and the improvement in marrow architecture and the peripheral differential produced by P^{32}.

We are well aware of the fact that single large doses, as at Hiroshima and Nagasaki, or chronic low doses of irradiation do increase the incidence of leukemia in both man and experimental animals.[158-160] However, it would seem impossible to

pears to be clear that more than 20 per cent of the patients with polycythemia vera have or develop an associated leukemia

In a study of 159 patients of this series, it was found that 111 (70 per cent) had a leukemic or leukemoid picture as evidenced by the presence of metamyelocytes, myelocytes, or myeloblasts in the peripheral blood when first seen by us Of these 111, only 20 had received previous x ray therapy and 7 previous P^{32} therapy Within this group of 111 there were eight cases in which the initial white count exceeded 20,000 (3 having had previous x ray and 1 previous P^{32}) and another group of 24 cases in which there were a positive differential an initial white count over 20 000 and an enlarged spleen, thus definitely leukemic in total picture It is interesting that 16 of the latter 24 had had no prior x ray or P^{32} therapy and the leukemia had no possible relation to radiation therapy

Four patients (2 5 per cent) had white cell counts above 20 000 but no abnormal cells In this connection we have observed that there is a direct correlation (r = 0 75) between the number of white cells and red cells in polycythemia vera,[17] and as pointed out above, the condition involves both the white and red cell series and platelets Following therapy there is a marked decrease in both the number of white cells and incidence of abnormal cells of the myeloid series in the peripheral blood Also, in more than one half of those patients who had a relapse with a rise in their red cell count subsequent to the first course of P^{32} therapy the white cell and platelet counts did not rise to levels as high as the original counts (see above)

Hall[6] reported 4 cases of acute leukemia occurring in 124 patients treated with P^{32} However since this report in 1949 these workers have not observed further cases of acute leukemia In the survival data of Videbaek [8] using older methods of therapy the average survival was only 4 5 years in males and 7 3 years in females and 3 out of 76 died of leukemia In a special study of 32 patients with polycythemia vera not treated with P^{32} Stroebel reported four deaths from chronic myelocytic

this was not true of the chronic leukemia cases It was interesting that these patterns persisted both early and late in the disease before and after radiation therapy in the presence of osteosclerosis and irrespective of clinical and laboratory findings suggesting transition to chronic myelocytic leukemia

Although there are no comparably large series of patients who have received neither x ray nor P[32] there are many isolated reports of polycythemia vera terminating in acute leukemia with no prior irradiation therapy [14, 162, 163*] Schwartz and Ehrlich[164] have recently reviewed the literature with reference to the incidence of leukemia in patients with polycythemia vera and found 83 cases They state however that only 30 of these had unequivocal evidence of polycythemia vera antedating the development of leukemia and only 5 of these had had no prior irradiation therapy This adds further evidence to the view that leukemia occurs as a natural complication Although the possible radiation induction in rare cases cannot be ruled out the extension of life and prevention of other complications outweigh this possible effect

Although P[32] has achieved remarkably good results in the treatment of polycythemia vera ultimately a better method of treatment will come after we have a better understanding of the mechanisms controlling red cell production Even though the results are excellent compared with those in many forms of cancer (Fig 21) they are not a completely satisfactory answer to the control of this disease In general radiation of any sort would not seem to be the ultimate answer to any hyperplastic or neoplastic disease Furthermore one hopes to protect individuals and masses of the population from radiation either in small doses delivered over long periods of time or single large doses and one does not like to administer any form of radioactive isotope to individuals over a period of many

* Wasserman[132] also cites two cases of polycythemia vera terminating in acute leukemia without any form of therapy other than venesection reported to him by Dr Dameshek in a personal communication

answer the question as to whether small, infrequent doses of P^{32} increase the incidence of leukemia over that seen after other forms of therapy in a disease in which leukemia is prone to develop without a comparably large series of patients who have received no form of radiation therapy

*One of the largest recent experiences in the study and treat*ment of patients with polycythemia is that of Wasserman He emphasizes the fact that polycythemia vera is a condition in which the hyperplastic marrow expands to encompass the total marrow space at the expense of the fat cells, and that there is a panmyelosis with stimulation of all hematic and nonhematic cellular derivatives of the reticulum cell and that during the natural course of the disease a stage of myeloid metaplasia occurs which is followed by any of three later stages myelofibrosis early spent polycythemia with anemia or chronic leukemia, or acute leukemia indicating that acute leukemia spent polycythemia and myelofibrosis are all stemming from a common cell He states that leukemia and myelofibrosis with myeloid metaplasia should not truly be classified as complications but rather as stages of the natural course of polycythemia vera and that if they live long enough all patients with this disease will develop anemia and changes in the white cells and platelets with marrow fibrosis and extramedullary hematopoiesis if they do not succumb to true complications represented by hemorrhage or thrombosis

Valentine and associates[161] have obtained some interesting findings concerning the relationship of these conditions In terms of blood histamine unit leukocyte alkaline phosphatase activity and unit myeloid leukocyte glycogen they found highly consistent biochemical patterns in chronic myelocytic leukemia and in polycythemia vera associated with a leukocytosis and moderate shift to the left The blood histamine of the polycythemia vera patients was high as was true of chronic myelocytic leukemia However the leukocyte alkaline phosphatase activity and myeloid leukocyte glycogen were markedly elevated and

distance of 1 cm in tissue containers and syringes should be made of material which will absorb all of these beta rays If this is not done it is possible for the individual handling this material over a period of years to accumulate irradiation particularly to the extent sufficient to bring about delayed changes and even neoplastic changes in the skin Furthermore P^{32} is radiation therapy and when such therapy is administered a powerful agent is being used One should always ask this question Is such therapy really indicated or is the patient one of those who might possibly be handled safely by infrequent venesections

Life Expectancy and Causes of Death

For the first time since 1938 when we introduced P^{32} in the therapy of this syndrome [83] it is now possible to analyze a sufficiently large series to make a statement regarding life expectancy From an analysis of 158 living and 73 deceased patients who have been under our care one can compute the percentage of the group who remain alive at each time interval from onset of the disease * using as a group total all those who have died plus all who have had an opportunity to live to the time under consideration We then have a set of data from which can be calculated a median survival time This figure will be a more reliable one than the mean longevity of the 73 deceased cases because it permits the use of living cases of unusually long duration yet does not bias the mean by including a number of

* Calculated by the method of W R Best and L R Limarzi (Am J Med 19 607 195[illegible]) and J T Litchfield Jr (J Pharmacol & Exper Therap 97 399 1949) The actual date of onset is not easy to determine In this study a disinterested observer determined the date of onset from examination of the patients charts and it usually coincided with the date of positive diagnosis except in a few cases in which it seemed clear from signs and symptoms that onset antedated diagnosis to an appreciable degree Our figure of 52 years agrees with that found for other large series and is only 1 2 years less than the figure for our age at first definite diagnosis

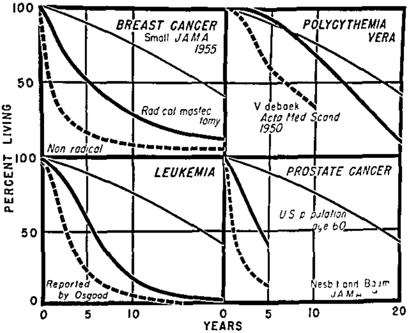


FIG 21 —Survival in cancer leukemia and polycythemia vera compared with normal life expectancy (thin line) Under polycythemia vera the dotted line represents the life expectancy after conventional methods of therapy and the thick black line our results after treatment with P^{32} For leukemia the thick black line depicts life expectancy in our patients with chronic lymphatic leukemia treated with P^{32} (Lawrence[208]) compared with average results in chronic myelogenous and lymphatic leukemia reported in the literature (dotted line)[209] Under prostate cancer the dotted line shows results before and the thick black line after the orchiectomy and diethylstilbesterol method of treatment developed by Huggins

years Although we have been unable to observe any definite deleterious delayed effects from administration of P^{32} to these patients, nevertheless there is little question that if large numbers of people are exposed to doses of radiation for many years there will be damaging effects

A note of caution should be added with reference to the storage and handling of P^{32} by the technician nurse or physician Since P^{32} emits beta rays which penetrate a maximum

TABLE 2

Age at onset	Average age	Number of cases	Mean survival (years)	Survival 5 years (per cent)	Survival 10 years (per cent)
18–43	36	56	18.6	95	88
44–52	48	56	13.[illegible]	93	70
53–60	[illegible]	57	12.0	93	67
61–80	[illegible]	61	9.7	86	47
18–80	52	231	13.3	92	[illegible]

These 231 cases include all deaths and some of these were in patients who prior to therapy with P³² had complications which had already limited their life spans (e.g., extensive thromboses).

for the relatively satisfactory treatment of this condition has taken 18 years to acquire since the introduction of this therapy in 1938. The first patient treated is living and well. Although we have follow-up information on the present status of 93 per cent of the patients, it has not always been possible to supervise closely their subsequent course, and we think the end results can be improved upon if supervisory control of the patient can be maintained. Based upon our experiences with this large group, we cannot emphasize too strongly the necessity for careful and frequent follow-up so that the total red cell volume and platelet count can be kept at normal or near normal levels to avoid complications such as hemorrhage and thrombosis. We have not always been able to get patients to return at frequent enough intervals to achieve this end. We are certain that such closer supervision will give better results than reported in the present series.

There were 16 patients who died with leukemia, of whom 6 had chronic myelogenous leukemia terminating in acute leukemia (as usually occurs in chronic myelogenous leukemia), [illegible] had chronic myelogenous leukemia terminating in subacute leukemia, 3 had a picture morphologically like that of chronic myelogenous leukemia, and in the other 2 the type was not clear. Eight patients died of cerebral hemorrhage, 1 of massive

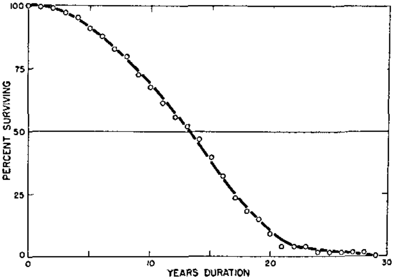


FIG 22—Percentage survival in 231 cases of polycythemia vera treated with P^{32} based on 73 deceased cases plus those living who have survived at least to the time for which the percentage is calculated Contact with 15 cases has been lost but their durations are measured only to the date at which they were last known to be alive The median survival is shown to be 13 3 years

persons who have not had an opportunity to live more than a fraction of their future life In this series of 231 cases the median survival is 13 3 years (Table 2 Fig 22) This figure can be contrasted to 6 7 years in a series treated by miscellaneous methods other than P^{32} (calculated from the data of Videbaek[8]) indicating the superiority of P^{32} in the treatment of this condition The difference in the average at onset and average age at definite diagnosis in our series is only 1 2 years so the above comparison can be made

Thus at present the life expectancy for patients with polycythemia vera is only a few years under the normal for the age group in question and is in the range of that reported for diabetics treated with insulin and patients with pernicious anemia treated with liver[165,168] This first statistical evidence

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44-52	48	56	13.5	93	70
53-60	56	57	12.0	93	67
61-80	65	61	9.7	86	47
18-80	52	231	13.3	92	68

* These 231 cases include all deaths and some of these were in patients who prior to therapy with P^{32} had complications which had already limited their life spans (e.g. extensive thromboses).

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TA LE 3—P t Mo t m F d g

N m	Ag s t d th	H t	Spl	L er	K d y	B e ma w	Ott er	Death
A B	60	450 Gm	5000 Gm f rct n d ec o- is uppe t aspe t	3000 Gm l k m c	R 350 Gm leukem L 2 0 Gm	Le k m c	Le kem e nfiltrat f l ng lymph nodes sk n l o	Le k m ac t my log n s
E B	81	410 Gm L V nt 18 mm	360 Gm w th h m t p et foc	N m l	N ph os l sis	I m l ype plastic		Ce et l farct d e to thr mbosi
C C	5	N m l	E l ged	E la g d	N m l	—		P r t n t s d et post perat pe f ti n f il um
J C		300 Gm	400 Gm ar h tec tur l ma k gs d t t	1100 Gm p t l ec osis nd a t lys of le- p t c c ll e- os of g ll bl dd w th ly al s f m t n	R 160 Gm L 160 Gm	My l s le osi.	C of tom ch itl m tast s t r t s. of bdom n os f sm ll b l res n l b oallg m t	S ba ute nd hron c holecyst tis w th l lel th s. Per f tion of gall bl d de w th bs n ter wall nd b t pe t n t s Te m nal b o lo- p um
T E	5	210 Gm	910 Gm l k m	2130 Gm l k mic	Le kem	Leuk		Le k m t
I F	65	480 Gm	10 Gm	1310 Gm	—	—		my l g no
R G	6	550 C L V t 5 mm	1210 Gm w th mye l d m t pl	F tty hlt t my l l m t pl a	N ph os l s	St m nd l l y pe pl t c		C gest l t f l C ngest e l t f l

C H		4 0 Cm	3 30 C m	610 C	N pl rosel oe	Le k m	Ch lery t d h f l tl uses g g m t	Leuk mia l k m my l gen w
N H	61	Norm l	N m l	—	Cl p l t	S m l ype plast		Pa ea t w h p l re tery hem- or hage
J I	49	500 Cm	1000 Cm	F l ge l	N p l l	S t l l ype plast	C neral ed t ro- l rc is	H m pe ic d m l t ru t d to m y ceel
O K	45	4 0 C m	930 C m 1 k m	000 C m f k m	N p h osel re			D nd al l w th l mor hage
M M	63	460 Cm	1800 C m 1 k m	6 0 C m l s- k m	Le k m	Le k m	Le k m filt t on f lymph odes	Le k m lu t my l ge us
S M	60	C o- y t os le- osis	800 C m	000 Cm	N p h sel is	t m l l m hy e plast t l m l		C bral gl l last ma
H M	2	N mal m t m al d lata- t f ght f ea t	1 50 C m 1 k m filtra t	1 00 C	125 Cm l	M kedly t p h e	Ace tes g ral d l ma m lt ple ec hym ses	Le k mia my l gen ou
F O	4	C o- ary t s le- rosis	E l ged	N m l	Ly l ph t m ll (25 Gm) d ff f lt t th lym phocytes			C great lea t f l ure gast leer l leed g
P I	66	90 Cm	3 0 Gm	1610 C m	B 310 C m L 300 C m	N t l n m l	M tastases t l gall l d l mesen t ry m t m pe t nea m lymph n des	A t pe t ta l w re ma g m d w th m tas tases)

T L 3—P t Mort m F d g

Nam	Ag s t d th	H art	Sp l	L	Kid ey	Bo m r w	Othe	Death
A B	80	450 Gm	5000 Gm f ct n a d nec o- pper t r s.pe t	3000 Gm le k m	R 350 Gm le k mi L 0 Gm	Le k m	Le kem filtrati n f lungs lym t nod k n l	Leukem a te my log n u
D B	81	410 Gm L t 18 mm	360 Gm w th l ema topo t c foc	N rm l	Neph os le osis	F m l ype plastic		C b l farct d e to th mbos
G C	5	N m l	E l rged	L l rg d	N m l	—		P ton t duct post pe t e pe f r t n of l um
J C	72	300 Gm	400 Gm ch tec tu l m k gs ind t n t	1100 Gm p t l nec osis d t lys of he- pat ll e- c os f g ll bladd w th ly bs es f m t n	R 160 Gm L 160 Gm	My los le os	C f t mach w th m t tases to ca t ss of bd men se s of m ll bow l o es d br ad l g ments	S b t d chron c h lecyst t s w th ch l l th as P f t n f g ll l d d w th bs es n nt wall nd ba te pe t n t Te m l b n bo- pn m n
T F	2	210 Gm	810 Gm l ukem o	2130 Gm l k m o	Le k m e	Le kem		Le k m t
I F	65	480 Gm	210 Gm	1340 Gm	—	—		myel g us C gest l ea t f l
R C	67	550 Gm L t 25 mm	1210 Gm w th mye- l d m t l	F tty filt t n my l d m t l	N l os l sis	St m d r b l y pe l a t		C gest l t f l

gastrointestinal hemorrhage, 10 with coronary occlusions, 10 with congestive heart failure. Of the 11 who died of carcinoma, 2 died of hypernephroma, 1 each of cancer of the pancreas, prostate, cervix, ovary, and kidney, 1 of melanosarcoma, 1 of multiple myeloma, 1 of cerebral glioblastoma, and 1 of lymphosarcoma. One patient died of pancreatitis with erosion of the phrenic artery, 1 cirrhosis of the liver, 1 malnutrition due to splenomegaly, 1 myelofibrosis, 1 of uremia, 1 chronic cholecystitis and cholelithiasis, and 1 of generalized arteriosclerosis. There were also 5 postoperative deaths recorded. This occurred in one case after a partial gastric resection, in 1 after an omental transplant, 1 after amputation of the leg for gangrene, 1 after splenectomy (this patient is also included in the myelogenous leukemic group), and 1 after perforation of the ileum following the freeing of intestinal adhesions which were producing an obstruction. In 7 patients we are unable to give the cause of death.

Before the introduction of P^{32} therapy, approximately 50 per cent of the patients died of either hemorrhage or thrombosis, and carcinoma, leukemia, and congestive heart failure were the other principal causes of death. In our group the incidence of death due to hemorrhage or thrombotic phenomena is about one half that reported by Videbaek and Stroebel et al. using venesections, phenylhydrazine, and x ray. This decreased incidence is undoubtedly due to better control of the total red cell volume and platelet counts in patients receiving P^{32}, thus minimizing the danger of hemorrhage or thrombosis.[4, 157]

Table 3 shows the significant postmortem findings in 21 patients, in 5 of whom the cause of death was attributed to leukemia. In 15 where the heart was weighed, 11 had enlarged hearts, in accordance with the observation that 50 per cent of the patients are hypertensive. In the 17 patients for whom the spleen weight was reported, it was enlarged in 14. Infarction and necrosis was noted in 1 case, myeloid metaplasia in 2, and

Table 3—C t n d

N m	Ag t d th	H t	Spl	L	Kid y	B em w	Other	D ath
C R	63	0 Gm l y p t rhy nd d l t t	350 Gm	860 Gm	R 30 Gm L 40 C m	—	G r l ei le k m filt t n ch n e l m hag ple t s byt oses	C gest h t f l u pulmo y g t on d e l m
G T	42	4 5 Gm	1 5 Gm	1600 Gm	N l	N m l ( )	A ute p n at t	D d n l lce post ope t gast oen t ost my l k ge
L V	9	430 Gm L Ve t 18 mm	1130 Gm w th my o d m t pl	000 Cm w th my l d n et pl	N m l	V t l Hype pla t e	I b m gast e r p- ll y d n e n n a of thyro d (e d tal)	C gesti e he t f l u e
D W	59	310 Gm	85 Gm	3 00 Gm v tl ma v m ta t t t m nod les	R 250 C m L 450 C m Ca f l ft kil y tl m tasta t r g l t k dn y	Hype pl xcept f l ft f m lere tl e w p t l pl d fib s	Met t to gl t d e al d l ft l e f	B l p um n d oc re m f kidn y w tl t t es
P W	5	L l g d	—	M t st	Hype n pl m	—	—	H n tho x d t l yper epl m

CHAPTER II

Relative Polycythemia

From time to time the author has had patients referred with the diagnosis of polycythemia vera who did not seem to fit the diagnosis. It was found that the increase in red cell count, hemoglobin and hematocrit was due to a low plasma volume with a normal total red cell volume.[17] This apparent increase in the number of red blood cells is seen in dehydration and also early after arrival at high altitude, although in the case of high altitude the relative polycythemia is later replaced by an absolute polycythemia. We have called this the relative polycythemia of anoxic stress.[22] The similar hematological picture in the patients referred to us with a diagnosis of polycythemia vera has been called by us the polycythemia of stress or stress polycythemia.[116]

The etiology of the condition in this latter group is unknown although, as will be pointed out, a significant number of the patients have background which would indicate unusual nervous stress or strain.[116] One patient (Table 4, B, C) had multiple myeloma.

There is no typical history. Some of the patients complained of dizziness. About half the patients were thought to have some significant anxiety situation or to be mildly psychoneurotic. This condition is found predominantly in the male. Of the first 31 patients seen, 28 were males varying in age from 16 to 75 and averaging 45. On physical examination 14 of the 31 patients were found to have the ruddy cyanosis characteristic of polycythemia vera. The heart, liver and spleen were not enlarged. Fifty per cent of the patients were overweight and 50 per cent were hypertensive. The usual laboratory studies showed only an increase in the red cell count, hemoglobin and hematocrit, but

leukemic infiltration in 4 (of 5 leukemic deaths) In 20 patients *where data are available on liver findings it was enlarged in 11* In 2 myeloid metaplasia was present and in 4 leukemic infiltration (of the 5 leukemic deaths) In 20 patients with description of the kidney available nephrosclerosis was observed in 6 in 2 there was chronic nephritis and in 3 leukemic infiltration Description of the bone marrow of the femur, sternum, rib vertebra or tibia was available in 15 cases, and hyperplasia was noted in 7 In one of these sternum rib and femur were hyperplastic but tibial marrow normal Myelosclerosis was noted in one or possibly 2 cases and the marrow was leukemic in 4 other cases Since the pathological information was usually obtained from patients under active therapy or in old age the the true pathologic picture was probably not seen

I O	M	16	67	65 5			110/62	5 68	16 8	300	390 000	55 8	27 0	28 5	40
C I	M	57	70	99 5	+	+	120/80	5 24	17 8	7 800	210 000	58 6	32 8	25 2	6
D S	M	32	0	89 5			148/105	6 15	18 5	7 100	180 000	56 6	30 6	26 0	11
H S	F	46		59 3			140 92	7 86	15 4	7 600	570 000	59 0	33 1	25 9	6
J S	M	46	6	81 8	+	+	124/98	1 90	14 2	15 500	150 000	57 7	28 0	20 7	19
J T	M	50		88 3			115/105	5 05	15 0	8 200	255 000	49 3	25 6	23 7	52
C W	M	18		79 1		+	118/72	5 90	16 7	6 900	420 000	65 4	36 0	29 4	55
C Wa	M	58	72	92			114/68	5 18	13 8	6 350	240 000	58 4	21 8	31 6	41
F Y	M	47	66	103 6	+		130/100	6 61	14 8	4 400	390 000	53 1	26 5	26 5	50
H Z	M	62	59	76 8	+	+	185 85	5 49	15 8	7 130	260 000	57 7	33 5	21 2	58

TABLE 4—*Hematological Data of Relative Polycythemia Patients*

Name	Sex	Age	Ht (in.)	Wt (kg)	Obesity	Ruddy	B P	RBC	Hgb (Gm)	WBC	Platelet	Blood volume data (ml/kg body wt) Total	TRCV	Plasma vol	Hmt
J A	M	44	72[1]	96 0	+	+	130/85	6 54	18 1	14 900	270 000	51 8	28 5	23 3	55
B B	F	68	62½	56 7		+	260/140	6 52	17 4	10 200	380 000	45 4	25 0	20 4	55
J Ba	M	43	72	81 4			150/78	6 04	15 0	10 900	260 000	54 4	26 1	28 3	48
J Bu	M	39	76	135 4	+	+	125/75	6 04	17 1	10 100	360 000	52 1	23 4	27 6	45
S B	M	56	58	68 2	+		155/90	5 78	16 5	5 900	250 000	67 4	34 7	32 7	52
B C	F	65	56	47 2		+	182/98	4 95	17 5	15 000	350 000	52 6	27 0	25 6	51
R C	M	44	71	95 [illegible]	+		150/90	5 26	15 4	9 600	230 000	58 8	31 7	27 1	54
J D	M	39	70	93 2	+	+	155/11[illegible]	7 36	17 5	8 000	240 000	52 4	26 7	25 1	51
B F	M	29		84 1	+		130/92	4 68	14 8	11 400	260 000	58 7	31 1	26 7	53
L F	M	51	66	67 5			130/90	4 68	17 6	6 000	200 000	57 9	31 8	25 8	55
R F	M	59	69	74 1		+	142/82	5 76	14 6	7 800	440 000	61 4	30 7	30 7	50
B C	M	57		106 4	+	+	160/94	5 26	16 7	5 800	200 000	51 9	30 1	21 8	48
F C	M	26	72	76 8			140/80	5 78	16 6	6 600	320 000	54 4	28 4	25 6	52
H C	M	75		68 6			138/88	5 40	16 0	13 700	570 000	52 5	28 0	24 0	69
W C	M	64	68	77 8	+		160/90	5 99	15 8	12 100	300 000	51 0	28 6	22 4	56
C H	M	65		62 7		+	110/70	5 16	15 2	9 300	340 000	57 0	28 5	28 5	50
G H	M	30	73	59 2			118/80	7 02	16 2	8 700	280 000	71 2	39 1	32 1	55
H H	M	53	70	84 4		+	160/112	5 72	15 2	5 650	225 000	64 [illegible]	41 6	22 9	59
M I	M	44		108 9	+		185/125	7 72	17 4	6 650	295 000	68 1	47 0	20 4	69
T L	M	41	67	83 2	+	+	130/98	5 37	15 6	7 200	310 000	51 7	26 8	27 3	49
F N	M	33	66	64 [illegible]			122/68	5 32	17 4	10 850	460 000	63 5	31 8	30 [illegible]	50

I O	M	16	67	[illegible]			110/6?	5 65	16 8	7 300	390 000	50 8	27 0	25 5	49
C I	M		0	99 5	+	+	120/80	5 24	17 8	7 500	210 000	59 6	32 8	25 2	36
D S	M	32	70	89 5			148/105	6 15	18 5	7 100	180 000	56 6	30 6	6 0	51
H S	F	46		59 3			140/90	56	13 4	7 600	510 000	9 0	33 1	21 9	6
J S	M	46	[illegible]	81 8	+	+	124/98	4 96	14 2	15 500	150 000	57 7	28 0	20 7	19
J T	M	50		55 3			145/105	5 65	11 0	8 200	255 000	49 3	25 6	23 7	52
C W	M	18		9 1		+	118/72	5 90	18 7	6 900	420 000	65 4	30 0	29 4	55
C Wa	M	58	72	92			114/68	5 38	13 8	6 350	240 000	6 4	24 8	31 6	41
F Y	M	47	66	103 [illegible]	+		130/100	6 61	14 8	4 100	390 000	53 1	26 5	26 5	0
H Z	M	42	59	74 8	+	+	155/85	5 79	15 8	7 130	200 000	57 7	33 5	24 2	8

TABLE 4 —*Hematological Data of Relative Polycythemia Patients*

Name	Sex	Age	Ht (in.)	Wt (kg)	Obesity	Ruddy face	B.P.	RBC	Hgb (Gm.)	WBC	Platelets	Blood volume (ml/kg body wt): Total	TRCV	Plasma volume	Hmt
J A	M	44	72½	96.0	+	+	130/85	6.54	18.1	11 900	270 000	51.8	28.5	23.3	55
B B	F	68	62½	56.7		+	260/110	6.82	17.4	10 200	380 000	45.4	25.0	20.4	55
J Ba	M	43	72	81.4			130/78	6.04	15.0	10 900	260 000	54.4	26.1	28.3	48
J Bu	M	39	76	135.4	+	+	125/75	6.04	17.1	10 100	300 000	52.1	23.4	27.6	45
S B	M	56	58	68.2	+		155/90	5.78	16.5	5 900	250 000	67.4	34.7	32.7	52
B C	F	65	56	47.2		+	182/98	4.95	17.5	15 000	380 000	52.6	27.0	25.6	51
R C	M	41	71	95.5	+		150/90	5.26	15.4	9 600	230 000	58.8	31.7	27.1	54
J D	M	39	70	93.2	+	+	155/115	7.36	17.5	8 000	240 000	52.4	26.7	25.1	51
B I	M	29		84.1	+		130/92	4.68	14.8	11 400	260 000	58.7	31.1	26.7	53
I I	M	51	66	67.5			130/90	4.68	17.6	6 000	200 000	57.9	31.8	25.8	55
R I	M	59	69	74.1		+	142/82	5.76	14.6	7 800	440 000	61.4	30.7	30.7	50
B C	M	57		106.4	+	+	160/94	5.26	16.7	5 800	200 000	51.9	30.1	21.8	48
I C	M	26	72	76.8			140/80	5.78	16.6	6 600	320 000	54.4	28.4	25.6	52
H C	M	75		65.6			135/88	5.40	16.0	13 700	570 000	52.5	28.0	24.0	60
W C	M	64	68	77.8	+		100/90	5.99	15.8	12 100	300 000	51.0	28.6	22.4	56
C H	M	65		62.7		+	110/70	5.16	15.2	9 300	340 000	57.0	28.5	28.5	50
C H	M	30	73	59.2			118/80	7.02	16.2	8 700	280 000	71.2	39.1	32.1	55
H H	M	53	70	84.4		+	160/112	5.72	15.2	5 650	225 000	64.5	41.6	22.9	59
M I	M	44		108.9	+		185/125	7.72	17.4	6 650	295 000	68.1	47.0	20.4	60
T I	M	41	67	83.2	+	+	130/98	5.37	15.6	7 200	310 000	51.7	26.8	27.3	49
I N	M	33	66	64.5			122/68	5.32	17.1	10 850	460 000	63.5	31.8	30.5	50

CHAPTER III

Secondary Polycythemia

Secondary Polycythemia, the result of an insufficient supply of oxygen in the blood, is commonly found in certain types of heart and pulmonary abnormalities and residence at high altitude. If one wishes to gain an intensive experience in the physiology of secondary polycythemia, he should go to Peru where there are over 165,000 people living between 14,000 and 16,400 feet in the Andes.[172] At no point in the United States can one find a permanent colony of people living and working at such heights. The author and his associates have carried out numerous studies in Peru, begun during two physiological expeditions to Peru in 1950 and again in 1952, and the latter studies are being continued in collaboration with Doctor Hurtado and his associates.

A. Polycythemia of High Altitudes

For many years the author and his associates have been interested in the physiological effects of reduced barometric pressure, particularly as seen in high altitude flight and in the low pressure chamber, and the physiology and treatment of various hematopoietic disorders, especially primary and secondary polycythemia, leukemia, and aplastic anemia as observed at sea level.[3, 4, 22, 16, 125, 18, 170, 171] Also we have been much interested in the general nature of how the animal and human body acclimatizes to high altitude. Consequently, for some time we had wanted to make certain special studies on native dwellers at high altitude for comparison with similar studies we have carried out on normal subjects and those with various abnormalities of the blood at sea level. It was our hope that we could shed additional light on the understanding of the effect of

blood volume studies with P^{32} labeled red cells showed that in all these patients there was a pathologically low plasma volume Studies of the rate of red cell formation with radioactive iron[135] showed that the rate of disappearance and the percentage uptake in the red cells in these patients were much different from that observed in polycythemia vera, and the amount of iron utilized was compatible with that required for a normal red cell production rate It is interesting to note that in these patients the white blood cell count was generally under 10 000 and that there were no abnormal white cells seen in the peripheral blood The blood oxygen saturation was normal This picture is similar in some respects to that which has been observed by Gaisbock, in which there is polycythemia with hypertension and absence of splenomegaly [19]*

Follow up studies of eight patients show that over intervals of from six to twenty four months during which time the patients did not receive specific therapy and were not phlebotomized, no significant change in the blood volume occurred That is the patients continued to have the pathologically low plasma volume with a normal total red cell volume resulting in a hemoconcentration Because of the fact that anoxic stress is known to produce a similar condition temporarily and because many of these patients were thought clinically to be under undue nervous stress and strain it is possible that this hemoconcentration may represent an effect of stress From the standpoint of therapy these patients should not be treated with any agent designed to reduce the total red cell volume Table 4 shows the pertinent findings in this group of patients

* Two cases described by Bassen may also fit this description (Frank A Bassen and Harold A Abel Pseudo Polycythemia J Mt Sinai Hosp 6 32? 1940)

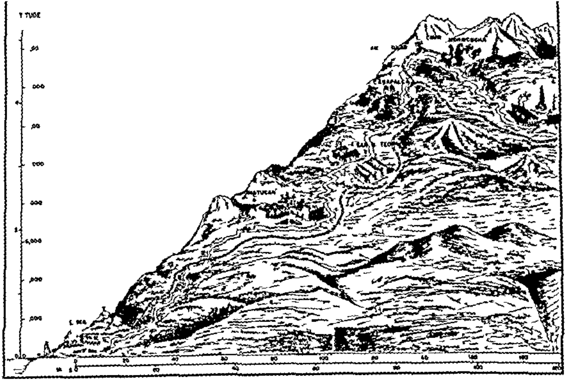


Fig 21.—Topography of site of studies in Lima and at Morococha in the Andean Cordillera (Courtesy of Dr Alberto Hurtado)

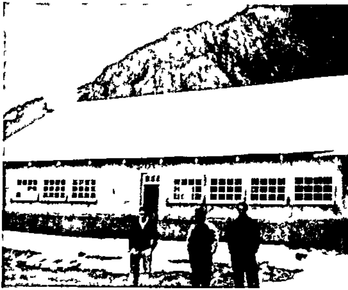


FIG 23 —The highest hospital in the world (15 800 feet) above Morococha Peru

acclimatization on bone marrow physiology and on the nature of the polycythemia which is an important factor in the acclimatization to the anoxia of high altitude and also on the nature of the disease polycythemia vera Our investigations [22, 138] were carried out in Lima * at sea level, at Morococha at an altitude of 14 900 feet and at a small hospital above Morococha Peru located at 15 800 feet, the highest hospital in the world (Fig 23) † At no point in the United States can one find a permanent colony of people living and working at such heights and where such studies as those described here can be carried out (Figs 24 25)

Since numerous and informative previous studies on the

* Through the kindness of Dr Alberto Hurtado of the Institute of Andean Biology we were able to work in his laboratories at Lima and Morococha

† Through the kindness of Dr Artemio Miranda industrial physician for the Ticlio Mine there

that time by numerous investigators In general with increasing altitude an increasing degree of polycythemia has been observed[20, 21] The most extensive studies have been those of Hurtado and his associates[20] on native Peruvian Indians These have clearly described the condition as being one in which there is a concomitant increase in red cells hemoglobin and red cell volume proportional to the altitude of residence without enlargement of the spleen or increase in white blood cells or platelets which are so commonly observed in polycythemia vera There is considerable evidence that increases in oxygen tension in the inspired air effect a net loss of red cell mass by inhibiting the marrow output of red cells[21, 11, 182] which is not true of primary polycythemia[110] Similarly there is evidence that decreasing oxygen tension exerts an effect such that there is a net gain in circulating red cell mass However Merino[15] and Delgado[13] have noted changes in urobilinogen excretion and serum bilirubin levels which could be interpreted as indicating that differing rates of destruction of red cells exerted a decided influence in the net changes of red cell volume with changes in barometric pressure and oxygen tension

High Altitude Studies

Three groups of subjects were studied first One was made up of 14 healthy medical students from the University of San Marcos (Lima) the second comprised 11 normal natives from the region of Morococha Peru and the third group consisted of 4 native miners living at Morococha who not only had polycythemia of high altitude but also suffered from pulmonary silicosis Each of the first two groups was studied in its normal habitat and then all of the studies were repeated at various periods of time after their arrival at the new altitude The trip from Lima to Morococha requires about four hours by automobile and the shortest period of acclimatization of sea level dwellers to high altitude before their repeat studies were done was twelve hours Other intervals of acclimatization of

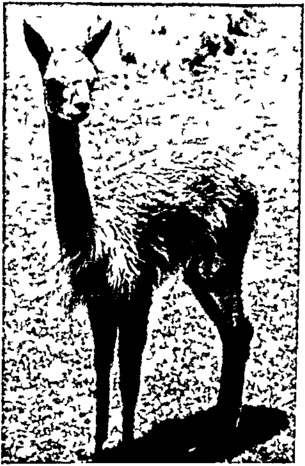


FIG 25—A vicuna an animal native to the Peruvian highlands Its polycythemic blood has an extraordinary capacity for combining with oxygen allowing it to be very active at these altitudes[203]

effect of altitude and anoxia on the animal and human have been carried out[20 173 179] either at altitude or in the low pressure chamber we had no intention of repeating these

The polycythemia of high altitude was first suspected by Paul Bert[178] and demonstrated in the inhabitants of Bolivia by Viault[180] and there have been many further studies on it since

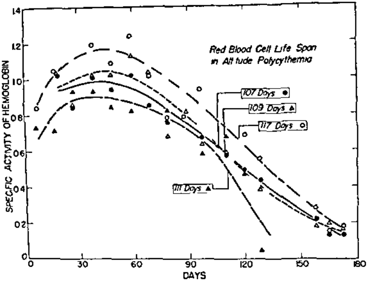


FIG 26A —The red cell life span in natives with polycythemia secondary to residence at high altitude No lengthening of the life span is observed [37]

carried out using scintillation counters developed by Anger [137] The plasma iron turnover rate constant was obtained by the method of Huff et al [135]

Table 5 contains the age height weight and chest measurements of the students and natives Chest measurements were made in a lateral and antero posterior diameter at the level of the mid axillary line and the xiphoid process in the midline respectively The circumference was measured at the nipple level when the subject was breathing normally at full expiration and at full inhalation The table gives the average values of these various measurements and in addition the averages of the same measurements of four Morococha natives having pulmonary silicosis and severe polycythemia No unusual findings were observed in the medical students The chest measurements of young natives serving as the acclimatized group were slightly greater than those of the medical students from sea level

this group were two four seven and ten days The shortest period of acclimatization of the Morococha natives at sea level was seven hours plus three hours required for the descent The longest period was ten days Additional intervals were two four six and eight days Numerous studies were carried out twice on each subject once in his normal habitat and again after his period of acclimatization at the different altitude The studies included history and physical examination complete routine blood studies blood volume blood oxygen plasma iron, plasma iron turnover rate, Fe^{59} uptake in the red cells,[135] and sternal marrow examination

Chest x rays were also taken of all of the Morococha natives and electrocardiographic data were made available on six of these natives through the kindness of Dr A Rotta and associates

A fourth group of normal subjects at Lima and a group of Peruvian miners living at 16 400 feet were studied from the standpoint of body water by the method of Siri using tritiated water [134]

Finally several groups of normal subjects at sea level at La Oroya (12 400 feet) and at Morococha (14 900 feet) were studied from the standpoint of red cell production with Fe^{59} and red cell life with the aid of C^{14} labeled glycine The latter studies were made in cooperation with Dr Hurtado and Dr C Reynafarje As can be seen by Figure 26A the red cell life span in four native Peruvian highlanders at altitude was normal [137] Similar studies on a group of Limeans normally living at sea level were made during their acclimatization at Morococha over 14 000 feet and these also showed normal life spans (Fig 26B) [137b]

The routine clinical and laboratory studies were carried out by accepted methods in general use The circulating red cell volume and blood volume were determined by the radiophosphorus tagged cell method of Berlin et al [17] Plasma iron analysis was done by the method of Kitzes et al ,[135] a modification of the method of Peacock et al ,[136] and the radioiron analysis was

two miners showed pulmonary fibrosis three of these were apparently due to silicosis

The complexion of most natives were typical of their race but in addition there was a pinkish blue color to the skin and mucous membranes not unlike that seen in severe cases of polycythemia vera but perhaps more cyanotic Evidence of venous and capillary engorgement was present over the malar eminences in the conjunctivae and in the retinal vessels The A V ratios of the latter appeared to be reduced in many cases although no exact measurements were made

Three students when moved to high altitude became ill within a few hours after arrival They had the following complaints anorexia nausea vomiting cephalalgia and asthenia The most severely ill student was pale and appeared extremely ill He had a persistent tachycardia and hypotension Two of the students were hospitalized at La Oroya (12 000 feet) for two days They made a good recovery after 2 days and insisted that they be allowed to complete their part of the study Nearly all students had some degree of anorexia during the first 3 days at Morococha

The four abnormal natives were brought to us because of their excessively high hematocrits These men had come to their physician because of various complaints such as bronchitis feeling of oppression in chest tachycardia (nocturnal) paresthesia of legs varicosities of legs hemorrhage from leg varicosities epistaxis and cephalalgia The physical examinations showed the following abnormalities conjunctival injection dilated venules in optic fundi cyanosis of hands (Fig 27) lips and ears mild clubbing of fingers hypotension tachycardia or bradycardia pulmonary second sound greater in intensity than aortic second sound and varicose veins of legs The referring physician Dr A Miranda who is Chief Physician of the Ticlio Mines has the information from long experience in caring for inhabitants of altitudes above 12 000 feet that they have an increased incidence of peptic ulcer and varicose veins also that

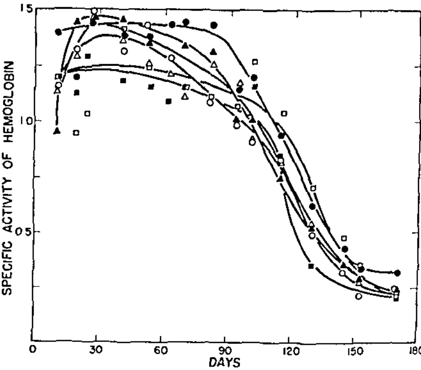


FIG 26B —The red cell life span in sea level dwellers in a study begun ten days after they were taken to 14 900 feet No lengthening of the life span was observed during acclimatization [176]

The four abnormal natives showed a more marked increase in chest size Both groups living at high altitude had relatively greater differences in chest size in the position of full expiration, indicating some emphysema The pulmonary second sound was consistently more intense than the aortic in the natives The chest x rays of the group of young natives although showing no evidence of silicosis, showed right heart enlargement Electrocardiograms (made available to us through the kindness of Dr A Rotta and his associates) of the natives showed right axis deviation The x rays of the four older na

Table [illegible] (Continued)

Lu	20	106	64 6	22	32	88	93	[illegible]
Ter	19	168	[illegible] 0	[illegible]	31	96	95	92
Rol	22	[illegible]	61 4	24	32	91	91	87
Rob	19	[illegible]	60 0					
Rim	20	110	[illegible]	23	28	89	92	87
Cir	19	162	[illegible]	21	30	87	89	84
Hut	21	[illegible]	[illegible]	24	31	94	97	92
Del	19	[illegible]	[illegible]	20	30	88	92	86
Average	[illegible]	113	61 [illegible]	[illegible]	31	90	91	88
Natives at normal (Morococha 14,900 ft.)								
Ca	[illegible]	[illegible]	[illegible]	21	30	96	9	91
Id	10	158	[illegible]	21	31	92	9	89
Ing	39	167	68 2	21	33	96	100	[illegible]
Cue	33	[illegible]	[illegible]	24	[illegible]	94	[illegible]	89
Average	42	161	61 [illegible]	21	[illegible]	94	97	91

TABLE 5 — *Anatomic Measurements and Ages of Students and Natives*

Name	Age	Height (cm)	Weight (kg)	Chest measurement A P at height (cm)	Chest measurement lateral (cm)	Chest measurement at rest (cm)	Chest circumference (cm)	Chest circumference (cm)
Students								
(Lima sea level)								
Sol	23	170	66.1	22	30	90	97	89
Tor	24	166	62.0	20	33	87	91	82
Cas	24	186	52.3	20	29	78	85	73
Fer	27	163	53.2	19	30	88	92	85
Ros	23	159	58.2	19	32	84	93	83
Piz	22	168	54.0	19	30	83	88	81
Rod	23	168	59.3	20	30	87	91	84
Cav	21	161	53.0	20	28	83	85	78
Pal	25	165	58.8	20	30	86	90	83
Flo	22	179	58.0	18	30	84	89	78
Mor	22	168	75.0	34	23	93	101	91
Feb	23	165	54.0	19	29	81	84	77
Pin	23	177	70.0	20	30	89	95	86
Average	23	169	59.4	21	30	86	91	82
Natives (Morococha 14 900 ft.)								
Ast	20	171	67.0	24	30	92	99	90
Sar	17	156	54.6	23	29	85	88	80
Bal	22	166	65.5	24	31	94	100	92

Table 6—Summary of Effects of High Altitude and Changes in Altitude on Hematological Values

	[illegible]		[illegible]		[illegible]
	A [illegible]	A[illegible]	A [illegible] 14,900 ft	Alt [illegible]	[illegible]
Hemoglobin Gm/100 ml	15.1 ± 0.8	16.5 ± 1.1	19.3 ± 1.9	18.0 ± 1.9	21.2
RBC × 10^6/mm^3	5.0 ± 0.1	[illegible] ± 0.5	6.7 ± 1.0	6.0 ± 0.6	[illegible]
Hematocrit	45.0 ± 0.2	48.0 ± 3.0	70 ± [illegible]0	55.0 ± 0.6	77.0
Reticulocytes (%)	1.[illegible] ± 0.[illegible]	2.8 ± 2.0	1.7 ± 0.6	1.2 ± 0.5	
Blood oxygen saturation (%)	97.0 ± 1.0	[illegible]9.0 ± [illegible].0	81.0 ± 3.0	9[illegible].0 ± 1.0	
Platelets × 10^5/mm^3	2.2 ± 0.6	1.8 ± 0.4	2.4 ± 0.8	3.2 ± 1.0	1.2
WBC × 10^3/mm^3	8.5 ± 2.1	9.[illegible] ± 1.7	[illegible].7 ± 2.2	[illegible].2 ± 1.8	6.4
Segmented cells (%)	54.0 ± [illegible].0	63.0 ± [illegible]0	[illegible]8.0 ± 9.0	[illegible]7.0 ± 11.0	
Band cells (%)	0.5	1.0	0.1	0.1	
Eosinophils (%)	3.0 ± 2.0	3.0 ± 2.0	2.0 ± 2.0	4.0 ± 4.0	
Basophils (%)	1.0 ± 1.0	0.5 ± 1.0	7.5	7.5	
Lymphocytes (%)	38.0 ± [illegible].0	29.0 ± 6.0	3[illegible].0 ± [illegible].0	3[illegible].0 ± 11.0	
Monocytes (%)	3.0 ± 2.0	3.0 ± 2.0	[illegible].0 ± 3.0	7.0 ± 2.0	
Blood volume (cc/kg body wt)	[illegible]0.[illegible] ± [illegible].1	62.3 ± 6.[illegible]	83.5 ± 16.8	80.2 ± 16.8	86.8
Total red cell volume (average)	3[illegible].0	[illegible]0.3	47.5	44.2	66.[illegible]
Plasma volume (average)	38.7	32.0	36.0	36.0	20.2
Nucleated red cells marrow (%)	23.5	32.0	29.9	31.0	
Plasma Fe in γ/ml	1.6 ± 0.4	1.8 ± 0.6	1.8 ± 0.6	1.9 ± 0.6	2.[illegible]
Plasma Fe rate constant	0.84 ± 0.09	1.13 ± 0.37	0.68 ± 0.10	0.43 ± 0.25	1.93
RBC uptake of Fe^{59} (%)	82.0 ± 9.0	86.0 ± 13.0	88.0 ± 12.0	63.0 ± 23.0	69.0
Fecal urobilinogen (mg/day)	87	85	68		
Height (cm)	165.5		162.8		161.0
Weight (kg)	59.4		61.1		64.[illegible]

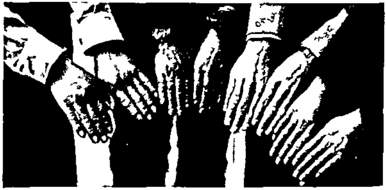


FIG 27 —Normal hands (second set from right) and those of natives of Morococha which show early clubbing and cyanosis

their life expectancy is considerably less than that of sea level dwellers There is as yet no statistical study on life expectancy and these and other similarly important questions need careful investigation

Peripheral Blood Findings

Table 6 summarizes the various hematological findings The average hemoglobin of the medical students in Lima was 15 1 ± 0 8 Gm per 100 cc of blood The normal natives at Morococha had an average value of 19 3 ± 1 9 Gm The ratio of the hemoglobin in the natives to the hemoglobin of the students equals 1 28 ± 0 05 [188] When the medical students moved to high altitude there was an immediate increase in the venous hemoglobin concentration In some individuals who were studied early after their arrival at high altitude this was almost as great as that shown by the subjects who had been at high altitude for 10 days When the natives moved to Lima, there occurred a questionable decrease in hemoglobin concentration and this again was evident only a few hours after descent Furthermore the decrease shown by those natives remaining at sea level for 10 days was little greater than that seen in those with short periods of acclimatization

TABLE 6—[illegible] [illegible]ary of Eff[illegible]ts of H[illegible]gh Alt[illegible] [illegible] and Ch[illegible]ges [illegible] Alt[illegible] on H[illegible] [illegible] Val[illegible]

	[illegible]		[illegible]		[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hemoglobin Gm./100 ml	1[illegible] 1 ± 0 [illegible]	16 [illegible] ± 1 1	19 3 ± 1 9	18 0 ± 1 9	21 2
RBC × 10⁶/mm³	5 0 ± 0 4	[illegible] ± 0 [illegible]	6 7 ± 1 0	6 0 ± 0 [illegible]	[illegible]
Hematocrit	4[illegible] 0 ± 0 2	48 0 ± 3 0	[illegible]7 0 ± [illegible] 0	[illegible] 0 ± 0 6	7[illegible] 0
Reticulocytes (%)	1 [illegible] ± 0 [illegible]	2 8 ± 2 0	1 7 ± 0 [illegible]	1 2 ± 0 [illegible]	
Blood oxygen saturation (%)	9[illegible] 0 ± 1 0	79 0 ± 5 0	81 0 ± 3 0	97 0 ± 1 0	
Platelets × 10⁵/mm³	2 2 ± 0 6	1 8 ± 0 4	2 4 ± 0 [illegible]	3 2 ± 1 0	1 2
WBC × 10³/mm³	[illegible] ± 2 1	[illegible] ± 1 7	7 7 ± 2 2	7 2 ± 1 8	6 1
Segmented cells (%)	[illegible]1 0 ± [illegible] 0	63 0 ± 7 0	[illegible] 0 ± 9 0	[illegible] 0 ± 11 0	
Band cells (%)	0 [illegible]	1 0	0 1	0 1	
Eosinophils (%)	3 0 ± 2 0	1 0 ± 2 0	2 0 ± 2 0	4 0 ± 4 0	
Basophils (%)	1 0 ± 1 0	0 [illegible] ± 1 0	[illegible]	[illegible]	
Lymphocytes (%)	38 0 ± [illegible] 0	29 0 ± [illegible] 0	3[illegible] 0 ± [illegible] 0	3[illegible] 0 ± 11 0	
Monocytes (%)	3 0 ± 2 0	3 0 ± [illegible] 0	[illegible] 0 ± 3 0	[illegible] 0 ± 2 0	
Blood volume (cc./kg. body wt.)	70 [illegible] ± [illegible] 1	62 3 ± [illegible]	83 5 ± 16 [illegible]	80 2 ± 16 8	[illegible]
Total red cell volume (average)	37 0	[illegible] 0 3	4[illegible]	44 2	[illegible]
Plasma volume (average)	38 [illegible]	[illegible] 0	[illegible] 0	36 0	30 2
Nucleated red cells, marrow (%)	[illegible]3 5	32 0	[illegible] 9	1 0	
Plasma Fe in γ/ml	1 8 ± 0 4	1 [illegible] ± 0 [illegible]	1 [illegible] ± 0 [illegible]	1 9 ± 0 6	[illegible]
Plasma Fe rate constant	0 [illegible] ± 0 0[illegible]	1 13 ± 0 3[illegible]	0 [illegible] ± 0 10	0 13 ± 0 2[illegible]	1 93
RBC uptake of Fe⁵⁹ (%)	82 0 ± [illegible] 0	86 0 ± 13 0	[illegible] 0 ± 1[illegible] 0	63 0 ± 23 0	[illegible] 0
Fecal urobilinogen (mg./day)	[illegible]	[illegible]	[illegible]		
Height (cm.)	166 5		1[illegible]2 [illegible]		1[illegible]1 0
Weight (kg.)	[illegible] 4		[illegible]		[illegible]

With reference to the red cell counts, the changes in each group as they moved to a new altitude paralleled the changes in hemoglobin concentration The same situation held with regard to the hematocrits of the two groups The average percentage of red cells which were reticulocytes in the medical students at Lima was 1 5 ± 0 5 and for the natives at Morococha 1 7 ± 0 6 whereas the average value of the students at altitude was 2 8 ± 2 0 and for the natives going to sea level 1 2 ± 0 5 The blood oxygen saturation studies carried out usually 3 hours after arrival at the new altitude are in general agreement with all previous studies on the blood oxygen at these altitudes There was a slight increase in the average platelet count of the natives when they moved from high altitudes to sea level and this increase was evident in the first few days of stay at Lima In the case of the medical students the average value for the platelets showed a possible decrease when they went from sea level to high altitude There were no significant changes in the total white blood cell counts The differential white cell counts of the natives both at Morococha and at Lima were not unusual but there is a suggestion that there is a slight increase in the percentage of the eosinophils in the natives when they moved to Lima whereas the percentage of neutrophils in the case of the medical students increased when they were moved from Lima to Morococha i e from sea level to high altitude The bone marrow studies brought forth some interesting changes The average percentage of nucleated red cells in the marrow smears of the 4 natives taken while they were at Morococha was 29 9 and of the 6 medical students in Lima 23 5 giving a ratio of the erythroid cells in the natives to that of the medical students of 1 27 In general the percentage of nucleated red cells decreased in the case of the natives when they descended to sea level and increased in the case of the medical students when they ascended to altitude With less than 1 day at sea level there was no change but in the 2 natives who were acclimatized for 8 days at sea level the values decreased from 37 4 per cent

to 21 2 per cent and from 30 0 to 18 2 per cent Conversely the percentage of nucleated red cells in the marrow specimens of the students was increased as early as the second day following ascent and at the seventh day the percentage of these cells was almost doubled

The average blood volume of the medical students at Lima was 4 2 ± 3 liters or 71 ml /Kg body weight After ascent to Morococha there was a decrease to 3 7 ± 4 liters or 62 ml Kg body weight The individual data show that this decrease occurred even in subjects who had been at Morococha for less than 1 day

The circulating red cell volume of students at Lima was 1 9 ± 0 2 liters or 32 ml Kg body weight and at Morococha 1 8 ± 3 Definite increases in red cell mass in individual cases after ascent were not observed since they did not remain at high altitude long enough to develop a true polycythemia

There was a definite decrease in plasma volume in the students following their arrival at Morococha the volume being 2 3 ± 2 liters in Lima and 1 9 ± 4 liters in Morococha These differences were evident in those cases studied the first few hours after arrival as well as those studied several days later

The decrease in blood volume after ascent could be accounted for entirely by the decrease in the plasma volume this also accounts for the increase in hemoglobin red cell count and hematocrit After returning from our first expedition to Peru we analyzed a group of patients referred to us with a diagnosis of polycythemia vera who were found to have this same syndrome i e increase in red blood cell count and hemoglobin no increase in red cell volume but a decrease in plasma volume (See Chapter II RELATIVE POLYCYTHEMIA) We now feel that in both groups this is a result of stress and is not a true polycythemia

The natives had an average blood volume of 5 1 ± 1 0 liters at Morococha and 4 9 ± 1 0 liters or 80 ml Kg body weight at Lima

With reference to the red cell counts, the changes in each group as they moved to a new altitude paralleled the changes in hemo globin concentration The same situation held with regard to the hematocrits of the two groups The average percentage of red cells which were reticulocytes in the medical students at Lima was 1 5 ± 0 5 and for the natives at Morococha 1 7 ± 0 6 whereas the average value of the students at altitude was 2 8 ± 2 0 and for the natives going to sea level 1 2 ± 0 5 The blood oxygen saturation studies carried out usually 3 hours after arrival at the new altitude are in general agreement with all previous studies on the blood oxygen at these altitudes There was a slight increase in the average platelet count of the natives when they moved from high altitudes to sea level and this in crease was evident in the first few days of stay at Lima In the case of the medical students the average value for the platelets showed a possible decrease when they went from sea level to high altitude There were no significant changes in the total white blood cell counts The differential white cell counts of the natives both at Morococha and at Lima were not unusual but there is a suggestion that there is a slight increase in the percentage of the eosinophils in the natives when they moved to Lima whereas the percentage of neutrophils in the case of the medical students increased when they were moved from Lima to Morococha i e from sea level to high altitude The bone marrow studies brought forth some interesting changes The average percentage of nucleated red cells in the marrow smears of the 4 natives taken while they were at Morococha was 29 9 and of the 6 medical students in Lima 23 5 giving a ratio of the erythroid cells in the natives to that of the medical stu dents of 1 27 In general the percentage of nucleated red cells decreased in the case of the natives when they descended to sea level and increased in the case of the medical students when they ascended to altitude With less than 1 day at sea level there was no change but in the 2 natives who were acclimatized for 8 days at sea level the values decreased from 37 4 per cent

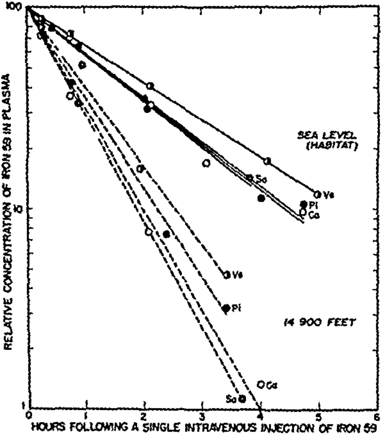


FIG 28 —The change in plasma iron clearance rates due to ascent to high altitude in 4 medical students normally living at sea level.

The average red cell uptake of radioiron in students at Lima 8 days after administration of iron was 82 per cent and in the natives at Morococha it was 88 per cent For the students at Morococha it was 86 per cent In the natives who had gone to sea level it decreased linearly with time of acclimatization to a value at 10 days of approximately 0 4 of that of the Morococha value (Fig 30) The radioiron uptake in the abnormal natives

The circulating red cell volume of the normal natives at Morococha was 2 9 ± 1 0 liters or 47 ml /Kg body weight, and at Lima 2 7 ± 9 liters or 44 ml /Kg body weight The ratio

$$\frac{\textit{Total Red Cell Volume Natives at Morococha}}{\textit{Total Red Cell Volume Students at Lima}} = 1\ 5 \pm 0\ 2$$

The plasma volume of the normal natives as calculated by the radiophosphorus method was 2 2 ± 3 liters at both Morococha and Lima The ratio

$$\frac{\textit{Plasma Volume Natives at Morococha}}{\textit{Plasma Volume Students at Lima}} = 1\ 0 \pm 1$$

The 4 subjects with silicosis showed the following volume data (Table 6) by P^{32} method blood volume averaged 5 6 liters or 87 ml /Kg of body weight red cell volume 4 3 liters or 66 ml /Kg body weight and plasma volume 1 3 liters or 20 ml / Kg

Iron Metabolism

Total plasma iron values were similar for both groups The average of the rate constants for the students at Lima was 0 54 ± 0 09 per hour whereas in the normal natives at Morococha it was 0 68 ± 0 10 per hour They represent the absolute values of the slopes of the lines in 4 individuals of each group of subjects in their respective habitats (Figs 28 and 29) The rate constants changed in the students a few hours after their arrival in Morococha and the difference was as great in some of the earlier periods as in the later ones The average value of the students following acclimatization was 1 13 ± 0 33 per hour in contrast to an average value of 0 54 ± 0 09 per hour in Lima (see Table 6) The change occurring in the plasma iron rate constant of the natives following their descent to Lima appeared to be a linear decrease with time (Fig 30) It is interesting to note that the average rate constant of the students at Morococha was considerably greater than the same constant of the natives living at Morococha

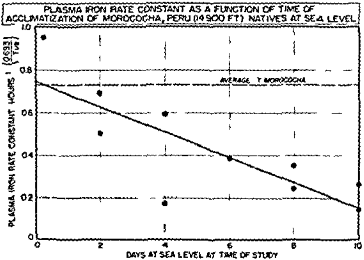


FIG. 30.—Plasma iron clearance rates as a function of time of acclimatization of Morococha natives at sea level

in blood volume, plasma volume and red cell mass. It would appear that in the case of the normal person going to high altitudes the early changes in the red cell and hemoglobin values can be attributed to hemoconcentration since there was a decrease in the plasma volume even in the very early periods after arrival at altitude. This is probably brought about through anoxic stress by some unknown mechanism and may be related to the so called polycythemia of stress discussed above which is seen at sea level. The changes in concentration of hemoglobin, red cells and white cells along with the morphologic changes in white cells seen in the first few hours after ascent simulate those seen in shock or in an alarm situation and probably the mechanism is the same.[188, 190] An increase in the concentration of plasma proteins has been reported by other investigators in relation to reduced barometric pressure,[191] exercise,[192] and epinephrine injection.[193]

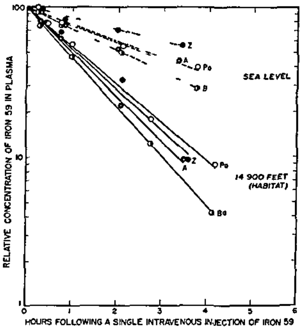


FIG 29 —The change in plasma iron clearance rates in 4 native Peruvian Indians on descent to sea level

was 69 per cent The red cell iron renewal rate changed with acclimatization at sea level more than any other quality examined For example the red cell iron renewal rate of the 2 natives having spent 10 days at sea level was only approximately 0 1 the value at Morococha showing the striking inhibition of red cell production like that seen in aplastic anemia

The 4 abnormal natives had average iron constants much the largest of any of the three groups studied but not as high as seen in patients with polycythemia vera [13, 139]

Discussion

The results of these studies on the physiology of acclimatization to altitude and to sea level and on the polycythemia of high altitude are of interest chiefly as they relate to net changes

increase in iron turnover and red cell production occurs immediately after arrival at altitudes as shown recently by Elmlinger et al. in studies in a low pressure chamber.[*] This change occurred more rapidly than the morphologic changes and was quite marked in contrast to the relatively small differences in the morphologic changes in the peripheral blood and bone marrow. These increased rates persisted throughout the ten days of study. The changes in the reticulocyte count did not parallel the increase in the iron rate but increased to a maximum on the seventh day and fell almost to normal by the tenth day. The increases occurring in the percentage of nucleated red cells in the marrow differential count did not indicate the extent of the increase in the turnover of iron in the marrow. The rapid increase in red cell production immediately after arrival at altitude as measured by Fe^{59} stimulated our interest in a possible humoral agent which might bring this about. This stimulus has led to the recent work on humoral and pituitary factors in erythropoiesis discussed above.

Examination of the data of other investigators in which acclimatization covered periods of 20 days or longer shows also that such an increase in the production rate of red cells is compatible with the measured increase in red cell mass. For example, Merino, studying 4 cases at Morococha from 18 to 21 days, found a circulating red cell mass 1.25 times that present at the beginning of the study. If this rate of twice normal were to continue for approximately 50 days in such subjects, they would at that time have very nearly the same red cell mass as the natives living at Morococha. The ratio, as was previously pointed out, is 1.5. However, if the rate continued longer than this, the red cell mass would go above that seen in natives normally living at high altitude. Thus it would be expected that the rate must decline eventually to a value of about 1.5 of normal unless such subjects actually carry a higher red cell mass than natives of the area. Data are apparently not available on the latter point. In the normal natives at altitude

The fact that we found no immediate increase in circulating red cell mass with ascent to 14 900 feet corroborates the findings of Hahn et al [194, 195] and Ross and Chapin[196] that all erythrocytes are in active circulation and are not trapped in the spleen or other organ for release to the circulation under stress

The relation of anoxia to increased endothelial permeability, edema exudation and increased lymphatic flow as demonstrated by Drinker[197] with respect to the hearts and lungs of dogs would seem to have considerable importance as an explanation of the hemoconcentration observed in subjects with short exposure to high altitude

Although Barcroft has demonstrated the remarkable capacity and contractility of the dog spleen[17, 176] and showed evidence of a high hematocrit in the spleen [177] as did Gibson et al [193] it appears unlikely that splenic contraction in man[193] contributes any more to hemoconcentration than other tissues in the body Using two independent methods P^{32} tagged cells and radioiron as a plasma diluent our results show a decrease in plasma volume sufficient to account for the rise in hematocrit red blood count and hemoglobin and are adequate evidence to rule out any sudden release or production of red cells as a factor in acclimatization to high altitude Peruvian natives of Morococha (14,900 feet) at rest show no decrease in plasma volume It would be interesting to know if foreigners of long residence at high altitude regained their plasma volume after their red cell volume had increased

Barcroft et al [199] commented on the rather great weight loss which they observed in themselves while they were at Cerro de Pasco We observed the same phenomenon It is not known that this weight loss is directly associated with the early occurrence of hemoconcentration During the early period of acclimatization it is probably chiefly due to loss of water [194, 207]

The plasma iron turnover rates were increased to approximately twice their normal value as were the red cell iron renewal rates in less than 12 hours at high altitude This marked

parabiotic animals Humoral regulation of erythropoie is now seems established with the isolation of specific erythropoietic factors (see previous discussion of hormonal and plasma substances)[54, 67]

The decrease in the iron turnover rates occurring when the Morococha natives moved to sea level simulates the very low iron turnover rates in patients with aplastic anemia[135] As pointed out above the reduction in red cell iron renewal rates after the acclimatization of the Morococha natives to sea level environment reduces these rates to approximately one tenth of their initial value Although many workers including Campbell[181] Hall[201] Pace et al[92] Tinsley et al[23] Hurtado et al[20] and others have shown that there is a decrease in the hemoglobin percentage and red cell values under exposure to increased oxygen pressure in normal animals or in normal subjects it was unexpected by us that the iron turnover rates would fall so markedly to levels approaching that observed in patients with aplastic anemia Finally the role of anoxia as a cause of the disease polycythemia vera as observed at sea level seems unlikely in spite of the similarity of the iron and red cell metabolism to that seen in altitude polycythemia since search of the records of the hospital of the Cerro de Pasco Copper Mining Corporation failed to reveal a single case of definite polycythemia vera

Summary

1 The rise in red cell count and hematocrit developing in the early periods after ascent to altitude is due to hemoconcentration

2 An increased or decreased rate in plasma iron turnover and subsequent incorporation of iron in red cells as measured with Fe^{59} is the most sensitive measure yet found for the detection of change in the rate of hematopoietic activity

3 A change in the rate of red cell production can explain the change in the number and volume of red cells resulting from

having a marked polycythemia, it is interesting to observe that they do not have a concomitant or compensatory decrease in plasma volume as seen in patients with polycythemia vera who have high red cell masses [17] However, in the case of the four natives who had pulmonary fibrosis a concomitant decrease in plasma volume was present In this connection there seems to be the interesting possibility that in altitude polycythemia there may be an increase in the number of open capillaries which allows for the marked increase in blood volume without decrease in plasma volume The present data are not conclusive however, with reference to this point

Although a relatively small group of bone marrow studies were carried out it is interesting that the ratio of the nucleated red cells in the bone marrow of the natives to the students in their respective habitats was 1 27, since approximately the same differences existed in the ratios of hemoglobin concentration red cell count and the plasma iron rate constant, the latter being 1 26 However the increase in the nucleated red cells series found in the 4 natives above that found in the students at sea level is not nearly as great as Merino and Reynafarje[29] found in their 16 examinations Our findings in the marrow of these natives are quite similar to the findings observed at sea level in polycythemia vera [30]

These studies definitely indicate that the immediate increase in red cell count and hematocrit on ascent to altitude is due to hemoconcentration and not to increase in the number of red cells However the known increase in red cell mass which occurs later and the normally high values of circulating red cell mass in natives of high altitude are consequences of an increased production rate and the rates of destruction are probably normal during this period of increase It is the consensus that this erythropoietic hyperplasia has as its stimulus hypoxia however that the mediation of this stimulus can occur without decreased oxygen concentration at the site of the hyperplasia has been well demonstrated by Reissman [60] in his studies of

counts are detailed in Table 7 for 3 patients (Patients J B S J and M S)

Pulmonary Disease Associated with Congestive Heart Failure There were 7 patients in this group with red counts ranging as high as 7 5 million at the time of initial observation and hemoglobin to 23 6 grams There was only 1 patient with a white cell count greater than 10 000 The platelet counts were within normal limits Blood volumes were determined on all 7 of these patients and all but 1 showed an elevation of the total red cell volume ranging from 38 8 to 57 4 cc /kg of body weight There was a distinct tendency for a low plasma volume in these patients Iron turnover in one patient showed a four times normal rate of production of red cells The blood oxygen saturation varied from 73 5 to 95 per cent The sternal puncture findings in 3 patients are detailed in Table 7 (Patients C J T P and W W) The spleen was palpable in none of them

Pulmonary Disease—Noncardiac The etiology of the pulmonary disease in these 10 patients is as follows One had metastases from a carcinoma of the kidney 1 a reduction in the amount of pulmonary tissue following a lobectomy 3 had bronchial asthma of long standing 4 were emphysematous and 1 had pulmonary fibrosis The total red cell volume was in the normal range in 1 in the high normal range in two others (32 4 to 38 2 cc /kg of body weight) while 6 showed marked elevation—57 6 58 1 and 58 8 cc /kg being the highest There was a distinct tendency for a low plasma volume so that the hematocrits in all these patients appeared to be higher than would be anticipated from the total red cell volumes The blood oxygen saturation was determined in 8 patients and ranged from 42–91 per cent saturated In 2 patients it was 90 3 and 91 These latter are at the lower range of normal The sternal puncture data on 3 patients are presented in Table 7 (Patients J P asthma L F emphysema and I M pulmonary fibrosis) The spleen was not palpable in any of these patients

variation in the oxygen in the inhaled air The life span of the red cell is not lengthened either during or after acclimatization

4 In agreement with the findings of others altitude polycythemia does not resemble polycythemia vera in that there is no concomitant enlargement of the spleen or thrombocytosis or leukocytosis

5 There is no evidence for an increased incidence of polycythemia vera among the Peruvian Indians living at high altitude

6 Ten days after descent from 14 900 feet to sea level the iron turnover in the native Peruvian Indian decreased to one tenth that observed in his native habitat This approaches that seen in aplastic anemia

B Cardiac and Pulmonary Types

This syndrome unlike polycythemia vera is the result of an insufficient supply of oxygen in the blood and occurs in certain types of heart and pulmonary abnormalities Recently we have carefully studied 26 such cases Seven had cyanotic congenital heart disease 7 had a long standing congestive heart failure with concomitant pulmonary physiological impairment 10 had non cardiac pulmonary disease and 2 had rheumatic heart disease

Cyanotic Congenital Heart Disease Of the 7 patients in this group all but one were adults The spleen was questionably palpable in 2 patients The red cell counts were elevated from 6 0 to 10 6 million with marked elevation of the hemoglobin (15 4 to 26 grams) Only 2 patients showed a white blood count above 10 000 and all had platelet counts within the normal range In 5 patients on whom the blood volume was determined the total red cell volume was found to be markedly elevated and in 4 cases was between two to three times normal All 5 patients had a considerable decrease in the plasma volume In 4 patients iron (Fe^{59}) turnover studies showed a red cell production rate from 2 to 3 times normal The blood oxygen saturation ranged from 73 to 85 per cent Representative sternal puncture

Rheumatic Heart Disease There were 2 patients with rheumatic heart disease Blood volume was not determined in either patient The blood counts were as follows (1) RBC 6 9 million hemoglobin, 13 0 grams platelets 520 000 WBC 6 600 reticulocytes 0 5 per cent segmented cells 45 per cent eosinophils 7 per cent lymphocytes 42 per cent and monocytes 6 per cent and (2) RBC 7 0 million hemoglobin 12 2 grams platelets 319 000 WBC 12 000 reticulocytes 1 5 per cent segmented cells 55 per cent band cells 7 per cent eosinophils 1 per cent basophils 1 per cent lymphocytes 28 per cent and monocyte 8 per cent Sternal marrow data are presented in Table 7 (Patients M I and I S)

As a group all of the e patients showed elevated red cell counts normal white counts and absence of palpable spleens Investigation of the blood volume showed elevation of the total

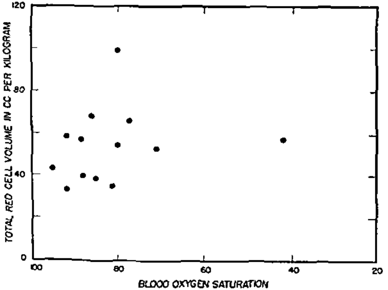


Fig 31 —The total red cell volume as a function of the blood oxygen saturation in secondary polycythemia

TABLE 7 —*Sternal Marrow Puncture Data of Secondary Polycythemia Patients*

	Cy t d g e t lh t			P lm arv d s a w th g t he t f l			P lm y d N d c			Rheum t he t d	
P t t	J B	S J	M S	C J	T P	[illegible]	J P	L F	I M	M L	F S
Segmented cell	24 4	11 6	10 0	30 6	15 8	15 4	33 4	21 6	13 2	12 6	29 0
Band cell	17 2	11 2	7 0	10 4	12 0	6 2	16 0	12 0	8 4	13 6	10 0
Metamyelocyte	2 6	2 8	4 4	0 8	1 4	1 0	2 4	1 6	1 6	3 2	5 0
Myelocyte	9 0	16 0	7 6	14 0	14 8	10 0	19 6	15 8	8 8	11 8	7 0
Eos myelocyte	0 4	0 4	0 6	1 4	0 2	2 8	0 2	0 6		0 4	1 0
Bas myelocyte		0 2						3 0			1 0
Progranulocyte	2 2	4 6		3 8	2 4	2 2	2 4		0 8		2 0
Myeloblast	0 6	1 0		2 8	0 2	1 6	0 6	2 0	0 8		1 0
Eosinophil	3 2	2 8	1 4	3 6	1 2	1 6	2 4		0 6	1 8	1 0
Basophil	0 6		0 2	0 4	0 2	0 2	0 2		0 6	0 8	1 0
Lymphocyte	3 4	12 0	4 8	11 6	5 2	6 6	3 8	14 4	4 4	4 6	19 0
Prolymphocyte										3 4	
Lymphoblast										0 4	
Monocyte			1 4	0 6		1 2	0 6				1 0
Normoblast	30 6	35 2	50 2	18 6	44 6	40 2	16 0	26 0	57 8	36 0	10 0
Erythroblast	0 4	2 4	10 0	0 8	0 4	2 6	0 6	1 8	2 0	5 6	5 0
Megaloblast		0 2	2 2	0 4		0 4				3 8	1 0
Plasma cell	0 4	0 6		0 2		2 0	1 2	1 0	1 0	1 6	2 0
Megakaryocyte								0 2		0 4	2 0

Summary

THE LITERATURE on polycythemia has been reviewed and physiological, clinical and therapeutic studies on 303 patients have been reported.

In *polycythemia vera* the most common symptoms are headache, dyspnea or orthopnea, dizziness, eye complaints and epigastric distress. The average age of onset is 52, the highest incidence being in the 60 to 70 years age group. The incidence ratio of males to females is 1.32. On physical examination ruddiness of the face and mucous membranes is found in 62 per cent of the patients, the spleen is palpably enlarged in 66 per cent and the liver in 33 per cent. Fifty per cent of the patients were hypertensive. White cell counts over 10,000 are common (75 per cent). The coefficient of correlation between the total number of circulating white cells and the total number of red cells is 0.75, which emphasizes the fact that it is a condition involving both the red and white cell series. The sternal marrow puncture findings are of limited value for diagnosis and evaluation of therapy, but sternal marrow biopsy is of great value. The blood volume is elevated as a result of a high red cell volume, but usually there is a decrease in plasma volume. The viscosity of the blood is increased. Studies with Fe^{59} indicate that much more iron is utilized than is needed for maintaining the high total red cell volume, while studies with C^{14} show that there are two populations of red cells, one with a normal life span and one with a short cell life. Thus it is a neoplastic like disease and is characterized by an increased rate of red cell production but with no lengthening of red cell life span. There is no evidence that bone marrow hypoxia is a cause of the hyperactivity of the marrow, but recent studies have demonstrated a humoral erythropoietic factor which may be the cause of the increased red cell production. Pulmonary

red cell volume and a decreased plasma volume The blood oxygen saturation was below normal Figure 31 shows the relationship between total red cell volume and blood oxygen saturation While there is considerable variation, the tendency for a progressive increase in the total red cell volume with decrease in blood oxygen saturation is evident and of course expected Iron turnover studies in this group showed a production rate of red cells that was several times normal but in general compatible with the total red cell volume assuming a normal red cell life span This iron turnover pattern was unlike that observed in *polycythemia vera, where the rate of production of red cells* may be two or more times more than that required to maintain the total red cell volume if a 120 day life is assumed The sternal marrow puncture findings show simply an increase in the number of nucleated red cells but do not permit differentiation from polycythemia vera usually As pointed out earlier sternal marrow punch needle puncture where pieces of marrow are obtained and sectioned does permit diagnostic differentiation In polycythemia vera there is hyperplasia of the other elements of the marrow i e megakaryocytes and young cells of the white cell series whereas in secondary polycythemia the hyperplasia is in the red cell series only

Case Histories (Polycythemia Vera)

Patient S. H.

This 61 year old white male was first seen here in 1945 when the following history was obtained. Chief complaints were dizzy spells, aches and drawing feelings in legs and arms, swelling of the ankles and a full feeling in the head which was not associated with true headaches, all of approximately 18 months duration. In 1944 severe cramplike pains occurred in the back and in December 1944 he first experienced dizzy spells. The symptom of chronic fatigue was severe enough at that time to make work impossible. On physical examination the patient had a ruddy cyanosis, congestion of the conjunctivae of the eyes and of the mucous membranes of the mouth. His blood pressure was 145/100, the spleen was enlarged approximately 6 cm below the costal margin and the liver was felt approximately 4 cm below the costal margin. There was pitting edema of the left ankle and foot. The blood counts and therapy are detailed in Figure 32. In 1945 the patient had venesections totaling 1,500 cc and approximately 9 mc of P^{32}. This therapy produced a satisfactory reduction in red cells, hemoglobin, white cells and platelets, and the patient remained in remission for nearly ten years. In September 1954 it was noted that his red count had risen to 6.72 million (from 4.5 million a year before), hemoglobin to 19.6 grams, white count to 18,600 and platelet count to 437,000. He was treated with phlebotomy and 3½ mc of P^{32}. This is an example of a patient who had a very satisfactory and long remission following one course of 9 mc of P^{32}.

Patient M. D.

This 52 year-old white woman was first seen by the author in 1945. The history revealed a decrease in feeling of well being since 1935 or 1936 with heaviness and aching in the arms. She had always been flushed in the face and in 1937 noted that her face had become blue and at one time there was a large hematoma of the left eyelid. In the early part of 1938 her condition was diagnosed as polycythemia vera, the red cell count at that time varying between 7.5 and 9 million, and thereafter until 1945 the patient was treated with frequent phlebotomies averaging about once a month; she also had had phenylhydrazine. In 1941 x-ray therapy to the spleen was given with symptomatic improvement; however, approximately three months after the x-ray therapy the spleen enlarged to an even greater size.

At the time the patient was first seen by us the principal complaints were

hyperoxia does not decrease the rate of formation of red cells as it does in secondary polycythemia

P^{32} therapy causes a reduction in total red cell volume and improvement in symptoms, decreases splenomegaly and blood volume, and prolongs life to near normal The incidence of leukemia is shown to be no higher than previously reported after other forms of therapy and probably is lower Before the use of P^{32} the most common cause of death was hemorrhage or thrombosis Marrow inhibition has reduced the proportion of deaths from these causes by about one half The average duration of life after onset in the whole series is near 14 years

Relative polycythemia is a condition primarily of males in the fourth or fifth decades and characterized by a pathologically *low plasma volume like that seen in dehydration About one* half the patients are obese and about one half hypertensive White cell and platelet counts are normal About one half show some overt nervous stress and strain These patients should not be treated with P^{32} since they have normal total red cell volumes This condition is not rare and can be mistaken for polycythemia vera It is also seen in individuals suddenly exposed to hypoxia but in this situation continued hypoxia leads to a secondary polycythemia

Secondary polycythemia occurs in individuals with cardiac or pulmonary disease or those who reside at high altitude It is characterized by elevation of the red cell counts and hemoglobin but no elevation in white cells or platelets There is no splenomegaly The blood volume is elevated due to an increase in the total red cell volume and as in polycythemia vera the plasma volume is usually decreased The blood oxygen saturation is low Red cell iron turnover studies show a red cell production rate that is several times normal but compatible with the total red cell volume unlike that seen in polycythemia vera *The life span of the* red cell is normal Secondary polycythemia is a normal physiological response to hypoxia and rarely should the polycythemia itself be treated

Case Histories (Polycythemia Vera)

Patient S H

This 61 year old white male was first seen here in 1945 when the following history was obtained. Chief complaints were dizzy spells, aches and drawing feelings in legs and arms, swelling of the ankle, and a full feeling in the head which was not associated with true headaches, all of approximately 18 months duration. In 1944 severe cramplike pains occurred in the back, and in December 1944 he first experienced dizzy spells. The symptom of chronic fatigue was severe enough at that time to make work impossible. On physical examination the patient had a ruddy cyanosis, congestion of the conjunctivae of the eyes and of the mucous membranes of the mouth. His blood pressure was 145/100, the spleen was enlarged approximately 6 cm below the costal margin, and the liver was felt approximately 4 cm below the costal margin. There was pitting edema of the left ankle and foot. The blood counts and therapy are detailed in Figure 32. In 1945 the patient had venesections totaling 1 500 cc and approximately 9 mc of P^{32}. This therapy produced a satisfactory reduction in red cells, hemoglobin, white cells and platelets, and the patient remained in remission for nearly ten years. In September 1954 it was noted that his red count had risen to 6.72 million (from 4.5 million a year before), hemoglobin to 19.6 grams, white count to 18 600 and platelet count to 432 000. He was treated with phlebotomy and 3.5 mc of P^{32}. This is an example of a patient who had a very satisfactory and long remission following one course of 9 mc of P^{32}.

Patient M D

This 52 year old white woman was first seen by the author in 1945. The history revealed a decrease in feeling of well being since 1935 or 1936 with heaviness and aching in the arms. She had always been flushed in the face and in 1937 noted that her face had become blue and at one time there was a large hematoma of the left eyelid. In the early part of 1938 her condition was diagnosed as polycythemia vera, the red cell count at that time varying between 7.5 and 9 million, and thereafter until 1945 the patient was treated with frequent phlebotomies averaging about once a month; she also had had phenylhydrazine. In 1944 x ray therapy to the spleen was given with symptomatic improvement; however, approximately three months after the x ray therapy the spleen enlarged to an even greater size.

At the time the patient was first seen by us the principal complaints were

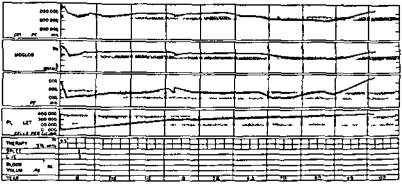


Fig 32 —Hematologic course of Patient S H

headache and nervousness Review of the systems showed that the patient's memory was poor and she was emotionally unstable given to crying There was aching in the arms and legs which was relieved by aspirin On physical examination she was a thin plethoric woman in no obvious distress The spleen was enlarged filling the entire left upper and lower quadrants and extending beyond the midline into the right upper quadrant It was slightly tender The liver was not palpable The initial blood counts are shown in *Figure 33 together with the therapy administered Two months after* P^{32} administration the patient noted that there was considerable symptomatic improvement with both subjective and objective evidence of considerable decrease in the size of the spleen At the same time a leukopenia developed

The patient returned in October 1946 by which time the red cell count had risen to the 9 million level and the white cell count was over 10 000 but the hemoglobin and platelet counts were within the normal range The spleen

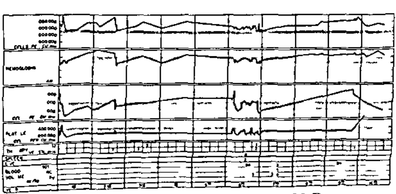


Fig 33 —Hematologic course of Patient M D

had enlarged to the midline and to the level of the umbilicus Seven venesections were carried out and a satisfactory reduction in the red cell count and hemoglobin resulted but no significant change in white cells or platelets In 1947 the patient had a venesection and 3 mc of P^{32} In November 1949 she again began to be fatigued which forced her to quit work as a sales clerk in a department store There was slight exertional dyspnea and swelling of the ankles in the late afternoon She complained of frontal and occipital headaches and pain in the eyes On physical examination the spleen was enlarged to the level of the umbilicus and to the midline In April 1950 the patient had an unusual neurological episode She could not use her hands they felt numb and her throat felt constricted so that she could not speak She also noted a sag in the right facial muscles and her local physician later stated that she had had a slight stroke These symptoms largely cleared during the first day and had disappeared three to four days later Physical examination two weeks later revealed a definite mild paresis of the facial muscles on the right and a slight deviation of the tongue to the right The patient then began to have attacks of vertigo Later in 1950 the vertigo hyperventilation and the same tight sensation in the throat recurred but cleared spontaneously in a matter of hours In the latter part of 1950 the patient had an aphthous stomatitis which responded very satisfactorily to antibiotics Following the administration of 3 mc of P^{32} in January 1951 the patient was considerably improved symptomatically She continued in good control although her spleen remained large until early 1953 when her red cell count rose again She returned for further observation in December 1953 complaining of a granulating ulcer on the medial aspect of the right leg with a large surrounding area of pigmentation of hyperkeratosis At that time her red cell count was 8 2 million hemoglobin 17 9 grams platelets 250 000 and WBC 16 900 Her red cell volume was 53 9 cc /kg of body weight She was treated with 3 mc of P^{32} which effected only a temporary reduction in her red cell count and a second dose of 3 mc of P^{32} was administered in September 1954

This is an example of a patient fairly well controlled in spite of periodic difficulty in following her clinical course

Patient H M

This 54 year-old white man was first seen by the author in 1941 In 1938 *following trauma it was found that he had an elevated red cell count* Three to four months after surgery for this trauma he began having aches and pains in his feet and his eyes began to bother him with blurring A diagnosis of polycythemia vera was made in October 1939 and he was treated by phenylhydrazine and phlebotomy until 1941 At the time neither the spleen nor the liver was palpable and there were no significant physical findings other than a florid complexion In July 1941 he was given 10 mc of P^{32} His course the

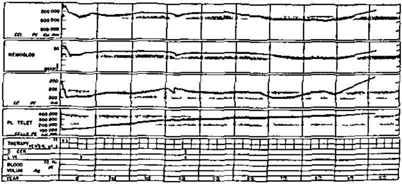


FIG 32 —Hematologic course of Patient S H

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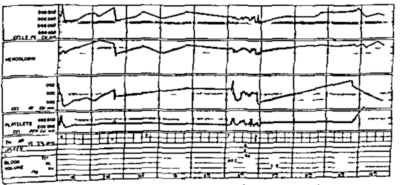


FIG 33 —Hematologic course of Patient M D

responded to therapy with P³² with a decrease in the white cell count and an increase in the red cell count and a decrease in spleen size. In 1950 the hematologic findings were those of chronic leukemia but in 1954 they are again normal.

Patient M. A.

This 46-year-old white male (see Figure 35) was a plumber by trade had been a native of Lithuania but had lived in South Africa for 18 years prior to being seen by the author in 1948. He was in good health until June 1947 when after strenuous exercise he noticed undue dyspnea and fatigue. Later *he noticed progressive weakness and a weight loss of approximately 30–35* pounds. During 1947 the patient noticed an increase in the size of a left upper quadrant mass. On physical examination he was found to be a thin dark skinned man who appeared weak. There was marked injection of the sclerae. The spleen was enlarged filling the entire left upper and lower quadrants and extending to the right lower quadrant. The liver was not palpably enlarged. The red cells numbered 8.9 million and the white cells 41,000 with many myelocytes. Blood counts and therapy are detailed in Figure 35.

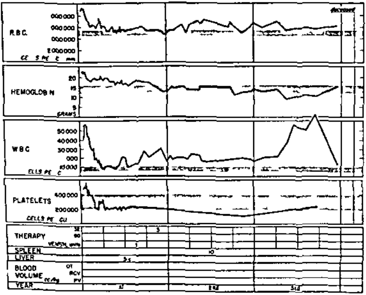


Fig. 35.—Hematologic course of Patient M. A.

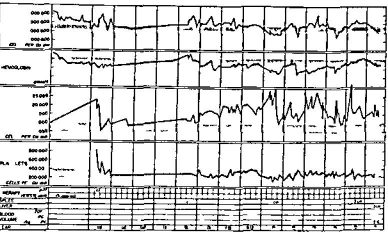


FIG 34 —Hematologic course of Patient H M

peripheral blood counts and the therapy are detailed in Figure 34 From 1942 to 1945 he was on active and vigorous duty as a Commodore in the Navy enduring many hardships during invasions without difficulty and had several venesections during this period of time The spleen first became palpable in July 1949 At that time the patient had a hematocrit of 38 with a total red cell volume of 21 8 cc /Kg of body weight The spleen continued to enlarge during the next few months and the patient was put on Feosol 1 tablet a day and 6 mg of testosterone sublingually per day In October 1949 he was hospitalized for sharp attacks of hip and shoulder pain which cleared up spontaneously In November 1949 the hematologic picture resembled that of chronic myelogenous leukemia and the patient was treated with a course of 4 mc of P^{32} his first P^{32} therapy since 1941 Following this the spleen became smaller and the white cell count decreased In November 1950 the patient had a gastrointestinal hemorrhage X ray examination showed a normal stomach and duodenum In April 1951 he had an episode of thrombophlebitis in his left arm The spleen continued to be palpable and his red cell count continued to rise During this period of time his white cell count which had been elevated to the 20 000–30 000 range was now down to the 10 000–15 000 range and in November 1952 he received 4 mc of P^{32} During 1953 the patient had an attack of gout treated satisfactorily by colchicine He has had no further P^{32} therapy up to December 1954 and his red cell count remains in good control

This case illustrates a satisfactory long term result following treatment with P^{32} and shows a very interesting period in 1949 when the patient had the hematologic and clinical picture of chronic myelogenous leukemia which

responded to therapy with P³² with a decrease in the white cell count and an increase in the red cell count and a decrease in spleen size In 1950 the hematologic findings were those of chronic leukemia but in 1954 they are again normal

Patient M A

This 46-year-old white male (see Figure 35) was a plumber by trade had been a native of Lithuania but had lived in South Africa for 18 years prior to being seen by the author in 1948 He was in good health until June 1947 when after strenuous exercise he noticed undue dyspnea and fatigue Later he noticed progressive weakness and a weight loss of approximately 30 35 pounds During 1947 the patient noticed an increase in the size of a left upper quadrant mass On physical examination he was found to be a thin dark skinned man who appeared weak There was marked injection of the sclerae The spleen was enlarged filling the entire left upper and lower quadrants and extending to the right lower quadrant The liver was not palpably enlarged The red cells numbered 8 9 million and the white cells 41 000 with many myelocytes blood counts and therapy are detailed in Figure 35

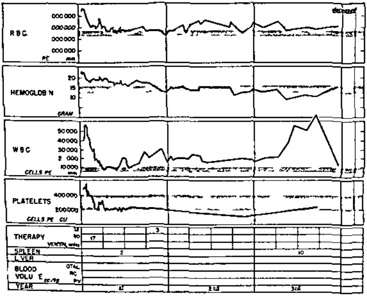


FIG 35 —Hematologic course of Patient M A

During P^{32} therapy the patient had a brief episode of bronchopneumonia which responded satisfactorily to antibiotics The red cells white cells hemoglobin and the platelets decreased The size of the spleen also decreased markedly so that instead of filling the entire left side it was palpable only down to the level of the umbilicus and appeared to be much smaller in its lateral diameter The patient returned home in July, 1948 and subsequent therapy was carried out by his referring physician Beginning in 1950 there was again some tendency for a progressive rise in the white cell count as when first seen by us and prior to any radiation therapy it that time with an increase in the number of metamyelocytes myelocytes and progranulocytes Anemia developed and the white cell count fell precipitously shortly before death and there was an increase in the number of immature myeloid cells present

This is an example of a patient who prior to therapy of any type had polycythemia vera with massive splenomegaly and also the picture of chronic myelogenous leukemia which two and one-half years later developed into acute myelogenous leukemia This case like a group of 12 others seen by us exhibited the picture of myelogenous leukemia prior to any form of therapy and demonstrates the fact that in polycythemia vera there is usually involvement of both the red and white cell forming tissues not brought on by P^{32} therapy

Patient L I

This 68 year old white female was referred with a diagnosis of polycythemia vera in 1949 Her chief complaint was loss of weight over the preceding five years with a 30 lb loss between 1947 and 1949 Since that time her weight had remained more or less stationary in spite of a good appetite and a large food intake During this time the patient had also been nervous In 1947 the spleen was found to be enlarged but no cause could be found There had been some occasional substernal burning at night which the patient associated with gas pains and which was relieved by belching She had not received specific therapy with x ray or P^{32} prior to being seen by us

Physical examination revealed a very thin woman with a sallow color Positive findings were A spleen that was enlarged into the pelvis and a liver reaching 4 cm below the right costal margin The blood picture revealed RBC 6 5 million hemoglobin 18 5 grams platelets 280 000 WBC 41 000 and reticulocytes 2 6 per cent The differential was segmented cell 64 band cell 8 metamyelocytes 2 myelocytes 3 progranulocytes 1 myeloblasts 1 eosinophils 4 basophils 5 lymphocytes 12 and nucleated red cells 4/100 WBC The sternal marrow puncture was unsatisfactory Urinalysis showed only an occasional white blood cell per high powered field

Nonprotein nitrogen was 48 mg per cent bilirubin 1 6 mg per cent total protein 7 25 grams per cent/100 cc A/G ratio 1 21/1 00 uric acid 10 mg per cent total cholesterol 123 mg per cent phenol ulphthalein 90 per cent excreted in 60 minutes A second bone marrow puncture showed 65 per cent normoblasts. Generalized increase in bone density was evident by x ray examination A bone marrow biopsy showed some increase in fibrous connective tissue with little fat present and relatively sparse hematopoietic tissue The blood volume was 100 6 cc /Kg of body weight total red cell volume 55 3

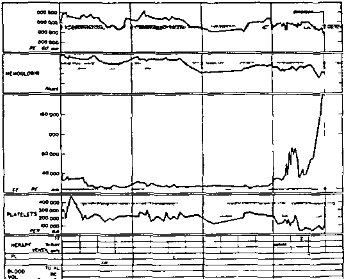


FIG 36 —Hematologic course of Patient L Y

TABLE 8 —*Blood Volume Studies in Patient L Y*

Date	Blood volume (cc/Kg of body wt)	Total red cell volume (cc/Kg of body wt)	Plasma volume (cc/Kg of body wt)
3-13-50	100 6	55 3	45 3
10-18-50	86 8	56 5	30 3
[illegible]-25-51	96 2	35 1	60 1
3-5-52	97 1	42 2	54 9
6-23-52	99 4	56 9	42 5

cc /Kg and plasma volume 45 1 cc /Kg The in vivo iron studies showed production of red cells in the spleen and no evidence of production in the bone marrow Her course and therapy are charted in Figure 36 and Table 8 In 1951 there was apparently a spontaneous decrease in the red cell count and total red cell volume the former being relatively too high because of an increase in the plasma volume Following this there was a rise in the total red cell volume so that by June 1952 the patient had a blood volume approximately the same as that determined on her first visit in 1949 During the Fall of 1952 the white count began a steady increase The differential counts continued to show increases in abnormal forms as had always been observed in this patient In December of that year platelet depression was observed The patient became increasingly cachectic in the next few months the spleen enlarged enormously and hemorrhagic manifestations were apparent For a brief period her physician obtained some slight subjective improvement with cortisone but the patient continued a downhill course and expired in May 1953

This is an example of a patient with myeloid metaplasia and myelofibrosis with leukemoid blood picture prior to any form of irradiation therapy

Patient H K

This 64 year old white male was first seen by us in March 1947 In 1936 his wife noticed that his eyes were very red An examination by his physician showed a reddened tongue and throat and a high red cell count The patient was then treated with phenylhydrazine but had an unsatisfactory response in that there was too great a decrease in the red cell count He was then treated by phlebotomy every eight weeks for the next six to seven years but the red cell count was never kept below the 7 0 million level during this interval

The initial physical examination revealed an athletic and well nourished man with a very markedly red complexion and cyanosis over the tip of the nose The spleen and liver were palpable Roentgen examination of the chest showed no abnormalities The initial blood picture was RBC 10 2 million hemoglobin 19 Gm platelets 220 000 and WBC 18 350 There were no abnormal myeloid cells in the peripheral blood The patient was treated with eight venesections of approximately 500 cc each followed by 3 mc of P^{32} Subsequent to this therapy the red cell count fell to slightly over 6 million but soon started to rise again and further therapy by repeated venesections and P^{32} was given The spleen decreased in size so that it was no longer palpable Figure 37 shows that from 1947 until early 1949 the patient had repeated venesections and received a total of 7 mc of P^{32} and 15 8 mc

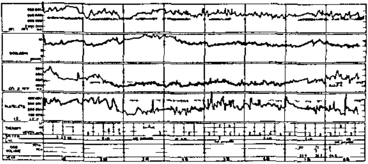


Fig 37 —Hematologic course of Patient H K

of Y^{90} colloid which in its effect is roughly equivalent millicurie for millicurie to P^{32} Following this the red cell count started to rise and he was again treated with venesections and P^{32} However it will be noted that the doses of P^{32} were much smaller than those given previously because the white cell count which had been in the 15 000–20 000 range was now in the 5 000–10 000 range The platelet count was also in the normal or low normal range When patients relapse the white cell count and platelet count often do not rise to the level seen previously Although the patient has continued to receive P^{32} and has had venesections up to the present time his red cell count continues to be approximately 6 million As a result of the repeated venesections the hemoglobin stays in the normal or lightly below normal range so that he is slightly hypochromic The white cell and platelet counts remain in the normal range With the exception of a persistent pruritis and an episode of gout which responded to colchicine this patient has been asymptomatic

This is a case illustrating a very difficult therapeutic problem since the patient has required very large doses of P^{32} and repeated phlebotomies to control the red cell count It should be pointed out that less than 5 per cent of the patients so far treated fall into the group that is extremely difficult to bring into a prolonged hematologic remission and this case history should be contrasted to those of patients S H M D and H M who have responded to treatment with much smaller doses at longer intervals He has been one of our most difficult patients to control satisfactorily yet from his own standpoint he has done very well

Patient A F

This 73 year old woman was first seen here in 1947 at which time her principal complaints were a feeling of fullness in the head exertional dyspnea

cc /Kg and plasma volume 45 1 cc /Kg The in vivo iron studies showed production of red cells in the spleen and no evidence of production in the bone marrow Her course and therapy are charted in Figure 36 and Table 8 In 1951 there was apparently a spontaneous decrease in the red cell count and total red cell volume the former being relatively too high because of an increase in the plasma volume Following this there was a rise in the total red cell volume so that by June 1952 the patient had a blood volume approximately the same as that determined on her first visit in 1949 During the fall of 1952 the white count began a steady increase The differential counts continued to show increases in abnormal forms as had always been observed in this patient In December of that year platelet depression was observed The patient became increasingly cachectic in the next few months the spleen enlarged enormously and hemorrhagic manifestations were apparent For a brief period her physician obtained some slight subjective improvement with cortisone but the patient continued a downhill course and expired in May 1953

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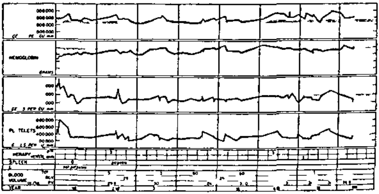


FIG 38 —Hematologic course of Patient A F

and easy fatigability with generalized weakness and some mental confusion Positive physical findings were a high color a blood pressure of 195/95 and a spleen palpable 1 fingerbreadth below the costal margin Her red cell counts were not excessive falling in the 5 5–6 0 million range The hemoglobin was low 9 3 Gm and platelet counts and white cell counts elevated The hypochromia was easily explained on the basis of her previous therapy which had consisted of almost monthly venesections of 500 cc for the preceding five years Other therapy had been x ray and phenylhydrazine to which the patient had responded unfavorably Her polycythemia had been diagnosed in 1939 Because of the high white and platelet counts the venesections were discontinued and P^{32} therapy instituted Her polycythemia was gradually brought into control with small doses of P^{32} and in general the patient has been well maintained on as little as 3 mc per year (Fig 38) Her principal symptoms at the present time are referable to her hypertension which her physician is now treating with Serpasil and Ansolysen with good result

This is an example of a patient with a persistent polycythemia that is not well managed by venesection As can be seen in Figure 38 conservative radiophosphorus therapy has reversed the hypochromia and thrombocytosis observed in 1947–48 and control of her red cell volume has been an important measure in minimizing complications such as hemorrhage and thrombosis which are apt to occur because of hypertension

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